The Autonomic Nervous System

ANATOMY, PHYSIOLOGY,
AND
SURGICAL APPLICATION

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THIRD EDITION

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Dedicated to

WILLIAM JASON MIXTER

Former Chief of the Neurosurgical Service

and to

ARTHUR W. ALLEN

Former Chief of the Peripheral Vascular Clinic
and of the East Surgical Service
of the Massachusetts General Hospital

First Printing, June, 1952

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FOREWORD

to the Second Edition

We are thrust into the world by smooth muscle, which is under control of the autonomic nervous system. From moment to moment we are dependent for our conscious existence on the moderate contraction of blood vessels, routinely kept in that state by autonomic impulses. Most of the complicated processes of digestion, from the initial outpouring of saliva to the final riddance of waste, require the participation of autonomic nerves. Any vigorous exercise in which we may engage depends upon co-operation of the autonomic government of appropriate effectors; thus, throughout eons of past time, the physical struggle for existence has been made possible by that government. And that government, furthermore, normally preserves, even to the stage of senescent decline, the stable states of the fluid matrix of the body that are required for ready response to every call for action.

Despite the essential role which the autonomic system plays in such fundamental services as continuance of the race, maintenance of effective relations with our surroundings, and provision for our sustenance and our fitness for effort, relatively little attention has been given, until recent times, to its natural modes of operating and to the muscles and glands through which it operates. For decades, eminent physiological investigators engaged in ingenious experimenting on striated muscle but paid slight regard to the functioning of smooth muscle. And efforts to explain glandular secretion were slighter still. Thus neglect of the agents of autonomic nerves accompanied meager attention to the structural and functional characteristics of the nerves themselves.

Only since the comprehensive studies of Gaskell and Langley were begun, about a half century ago, has much insight into the organization of the elements of the "involuntary" or "vegetative" nervous system been gained. Still more recently have the physiological values of the system to the organism as a whole been somewhat clarified, and its connections with the central nervous axis partially traced. At present, interest centers on the implications of the fresh discovery that autonomic impulses are transmitted to muscles

PREFACE

to the Third Edition

In writing the third edition of this book, the most difficult problem has been to incorporate, without unduly lengthening the text, the great mass of important data from wartime and civilian experience which has accumulated during the past decade. Many of the older references, as well as some of the case histories and illustrations, included in the two former editions have therefore been eliminated. The chapters on anatomy, physiology, clinical testing of patients, and operative technique have been extensively revised and brought up to date. All of the others have been virtually rewritten.

Since the publication of the second edition Dr. Smithwick has transferred from the active staff of the Massachusetts General Hospital and the faculty of Harvard Medical School to become Professor and Chairman of the Department of Surgery of Boston University School of Medicine and Surgeon-in-Chief of the Massachusetts Memorial Hospitals. Dr. Simeone was invited to take part in the preparation of this third edition because of his former association with Professor Cannon in the Department of Physiology at Harvard Medical School; because of his intimate knowledge of the patients on the peripheral vascular service at the Massachusetts General Hospital; and because of his study of vascular injuries in World War II—a study which he conducted overseas and as one of the investigators in the postwar follow-up carried out under the Veterans Administration and the National Research Council. Before he had completed his portion of the manuscript, he was appointed Professor of Surgery at Western Reserve University School of Medicine and Director of Surgery at City Hospital, Cleveland, Ohio. The clinical cases and statistics on which this work is based are therefore derived from the Massachusetts General and Massachusetts Memorial Hospitals in Boston and, to a lesser extent, from patients of the U S. Navy, Army, and Veterans Administration observed by White and Simeone during their period of military service and in their subsequent work for the National Research Council.

and glands by chemical substances, adrenaline and acetylcholine, which are the directly effective deputies of the nerve impulses.

Understanding of the highly significant role played by the autonomic system in the functioning of the body has opened new vistas. The ways have been revealed in which pain, cold, various emotional states, and other conditions which excite autonomic discharges can induce or participate in pathological processes. Thereby, morbid phenomena which have long been regarded as mysterious have received reasonable explanation.

Practical effects of advances in knowledge of the anatomy, physiology, and pathology of the autonomic system have been seen in both pharmacotherapy and surgery, especially in the latter. The opportunities of progressing beyond the boundaries of familiar surgery seemed to have been coming to an end. In being subjected to surgical skill, however, as in being subjected to comprehensive scientific study, the autonomic system suffered neglect. Here was a chance for pioneering, and it was taken. Leriche in France, Adson, and White and Smithwick in the United States have made impressive advances in applying surgical technique to the treatment of pathological states resulting from abnormal autonomic activity. White's earlier volume on the anatomy, physiology, and surgical treatment of the autonomic system marked an important step forward in summarizing both scientific information and its practical significance. In the present volume White and Smithwick have admirably gathered the latest knowledge of the structure and functions of the system, and reported from their own extensive experience and from the experience of others the methods by which surgery can be applied to the cure or mitigation of disorders of autonomic origin.

WALTER B. CANNON, M D.
Professor of Physiology
Harvard Medical School

1941

CONTENTS

For permission to utilize this valuable material we wish to thank the Surgeons General of the Army and Navy, the Veterans Administration, and Drs. Edward D. Churchill and Walter Bauer, chiefs of the surgical and medical services, respectively, of the Massachusetts General Hospital. We have also drawn freely on the laboratory and clinical departments of the Harvard Medical School and its associated hospitals for technical advice and additional clinical material. Of those who helped in the preparation of the former editions, we are still particularly indebted to Dr. Donal Sheehan, Professor of Anatomy at New York University, for his criticism of the historical chapter; the late Professor Walter B. Cannon of Harvard Medical School, Dr. Arturo Rosenblueth of the Instituto Nacional de Cardiologia of Mexico, and Dr. Robert S. Morison of the Rockefeller Foundation in New York for their advice in neurophysiology and anatomy; and Dr. Stanley Cobb, Chief of Psychiatry at the Massachusetts General Hospital, for his help with the portion relating to the central nervous system and psychological correlations. In addition, we wish to express our indebtedness and gratitude to many others who have made this work possible. Amongst the staff of the Massachusetts General Hospital particular acknowledgments are due to Drs. Paul D White, Edward F. Bland, and Chester M. Jones of the medical services; Drs. William Jason Mixter, Arthur W. Allen, Leland S McKittrick, Robert R Linton, and Joe V Meigs of the surgical services; Dr Henry K. Beecher and other members of his staff in anesthesia; and to Drs Kenneth A Evelyn, William P. Chapman, and Robert S. Palmer of the committee for the study of hypertension. At the Massachusetts Memorial Hospitals, Drs. George P. Whitelaw, Charles W Robertson, Douglas A. Farmer, and Jesse E Thompson have prepared clinical and statistical material.

Acknowledgment is made in the text to many authors and publishers who have kindly permitted us to reproduce passages and illustrations from their articles. It is impossible to thank all who have contributed to the preparation of the manuscript, but we feel especially indebted to our secretaries, Miss Lucy Allen, Miss Elizabeth Egan, and Miss Adele Khoury, for their patient and devoted work; and to Mrs Muriel McLatchie Miller, Mrs. Edith Tagrin, and Mr. William O'Leary, the medical artists who have produced the drawings and charts.

ILLUSTRATIONS

PART III

LIST OF TABLES

CHAPTER I

Introduction

The first edition of this monograph, which appeared in 1935, was written at a time when surgeons were just beginning to understand the effect of interrupting the cardiovascular and other visceral nerves. The subject had to be approached with the realization that much of what was set down would require revision. As predicted, understanding of function and the therapeutic possibilities of surgical intervention have both advanced at such speed that extensive revision was necessary in 1941, and now, after another lapse of ten years, an even more complete rewriting is called for.

This third edition, like its predecessors, is written for students of neurology as well as for those who are concerned with the practical application of neurophysiology to disordered visceral function and intractable pain. In order to make it of the greatest practical value to the clinical investigator, as well as to the general practitioner and the surgeon, we have endeavored to gather into one volume the fundamental contributions of the anatomist, the physiologist, and the pharmacologist, as well as those of the internist and the surgeon. The increasing opportunities to modify abnormal visceral activity and sensation by neurosurgical measures require a fundamental approach to the concepts of visceral innervation. In no field of modern medicine has information derived from animal experimentation played a more vital role in clinical progress. The current literature is so vast that we have been able to mention only the more important articles, but the reader who is interested in any particular field can obtain a very complete bibliography by referring to these publications.

In the past many clinical articles have been written in a spirit of overenthusiasm so common to pioneer work and with inadequate follow-up studies. This, as we realize only too well, applies to past publications of our own, as well as to those of other workers in the field. We are happy to have this opportunity to point out past mistakes. Failure to obtain the results expected from reading descriptions of new forms of surgical treatment has been a discouraging experience of all surgeons who have worked in this field. In writing the following chapters, therefore, it is our intention to rely principally on experiences which have been extensively verified and to

CHAPTER II

The Historical Development of Knowledge of the Involuntary Nervous System

The earliest recorded reference to the visceral nervous system was made by Galen * in the second century. He gave the first account of the paravertebral sympathetic chains with their superior and inferior cervical and semilunar ganglia, but he made the mistake of describing the sympathetic and vagal trunks as one structure originating within the cranium. This gave rise to an error which persisted for fifteen hundred years. Galen was the first to note that the denervated heart maintained its beat, as he observed that hearts removed in animal sacrifices continued to beat in the hands of the priests. Following these observations of the great Greek physician, little progress was made through the ensuing fourteen centuries until the time of Vesalius (1543), who made dissections and diagrams of the sympathetic ganglionated trunks and some of the important peripheral plexuses. Like Galen, Vesalius (Fig. 1) depicted a combined vagosympathetic trunk arising from the brain stem. Stephanus (1545) and later Eustachius (1563) were the first to distinguish the two separate nerves, but in the Eustachian plate the sympathetic trunks arise from the abducens nerves. The copperplates of Eustachius' dissections made in 1552 were never published during his lifetime but remained in the papal library for a hundred and sixty-two years. Finally, Pope Clement XI presented the plates to his physician, Lancisius, who published them in 1714 (Fig. 2).

In the seventeenth century Willis (1664) published a remarkably clear account of the ganglionated chains and their connections with the intercostal nerves. He described the cardiac branches and stated that the great mesenteric plexus, placed in the midst of others like a sun, sent its nerve fibers like rays in all directions; hence, it came to be called the solar plexus. He considered that its function was to place the heart and viscera in connection with the brain so that they should act in harmony. The modern

* See *De usu partium corporis humani* (1550) and Daremberg's translation (1854).

discuss the bad as well as the good results observed at the Massachusetts General Hospital and at the Massachusetts Memorial Hospitals. In this way we believe that fairly definite statements can be made and defended on many of the therapeutic problems which are discussed A few, like the surgical treatment of essential hypertension, still require further evaluation, as reflected by differences of opinions of the three authors freely expressed in Chapter XII. The problem of modifying the activity of the visceral nervous system in man still remains a challenge to both the physiologist and the surgeon

Several monographs on the surgery of the autonomic nervous system have appeared, the earliest being those by Brüning and Stahl in 1924 and by Hesse of Leningrad in 1930. Both were written in German. Recent advances in physiology and neurosurgical knowledge have been so rapid that these books are now out of date. In England a good short monograph was published by Gask and Ross (1934), with a second edition in 1937, but this dealt with only a limited part of the field of autonomic neurosurgery and is also outdated.

Among the more recent monographs the comprehensive texts of Pi Suñer (1947) and the Tardieus (1948) contain helpful reviews of the voluminous literature of recent years, particularly of Spanish and French work Modern physiological concepts of the function and organization of the autonomic system have been particularly well reviewed by W. R. Hess (1948), who won the Nobel prize for his contributions to this field. In addition to these texts, a valuable symposium on *The Vegetative Nervous System* was published by the Association for Research in Nervous and Mental Disease in 1930 and others on special subjects such as *The Hypothalamus and Central Levels of Autonomic Function* in 1940 and *Pain* in 1943. Reviews of progress such as Sheehan's (1941) and Hare and Hinsey's (1942) on physiology which have appeared in the *Annual Review of Physiology* and periodic reports on clinical progress by White in *Surgery,* Smithwick in *The New England Journal of Medicine,* and Livingston in *Confinia Neurologica* serve to make the more valuable recent contributions accessible.

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nomenclature of the cranial nerves originated with Willis. In addition, he gave an accurate description of the vagus or "wandering nerve," with a true understanding of its apparent union with the cervical sympathetic in some of the lower mammals and its separate course in man. He even noted the branch given off to the aortic arch, "so it may react to changes in the pulse." According to Sheehan (1936), who describes the conception of the auto-

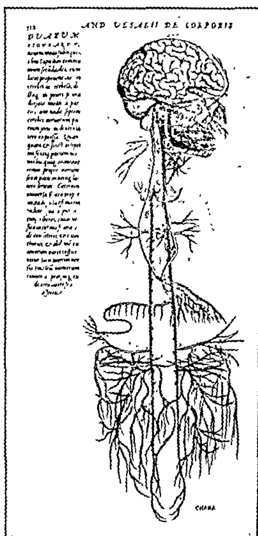


Fig. 1. Vesalius' illustration of the "sixth pair" of cranial nerves (according to Galen's classification).

The vagus nerve and the cervical portion of the sympathetic trunk are represented as one trunk. The thoracic and abdominal portions of the sympathetic chain and the rami communicantes are clearly shown (From *De humani corporis fabrica*, 2nd ed., Basel, 1555, p. 512, reproduced through the kind permission of Dr. John F. Fulton from the original now in the Yale Medical Library. Acknowledgment for legend is made to Sheehan, D. "Discovery of the autonomic nervous system." *Arch. Neurol. Psychiat.*, 1936, 35: 1081–1115, courtesy of American Medical Association, Chicago.)

nomic nervous system at the end of the seventeenth century, the "intercostal" (sympathetic) and "wandering" (vagus) nerves, though clearly separated anatomically, remained physiologically one system, possessing a double function. On account of its numerous intercommunications, it was

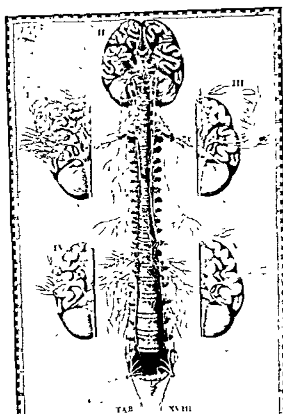


Fig. 2. Eustachius' conception of the cerebral origin of the cervical portion of the sympathetic trunk from the abducens nerve.

The separate course in the neck of the vagus nerve and the sympathetic trunk had by this time been recognized. The superior cervical ganglion and some of the lower sympathetic ganglia are shown. (From *Tabulae anatomicae*, Amsterdam, 1722. Copperplates made in 1552. Reproduced through the kind permission of Dr. John F. Fulton from the original now in the Yale Medical Library. Acknowledgment for legend is made to Sheehan, D. "Discovery of the autonomic nervous system." *Arch. Neurol. Psychiat*, 1936, 35: 1081–1115, courtesy of American Medical Association, Chicago.)

looked on as the *modus operandi* by which "sympathy" could be brought about between different parts of the body. When one stops to remember that this concept was based almost entirely on anatomical observations, it constitutes a most remarkable hypothesis.

In 1732 the Danish anatomist, J. B. Winslow, gave the name "sympathetic" to nerves which he demonstrated by dissection to lie outside the main cerebrospinal pathways. Neubauer (1772) published a superb illus-

tration of the vagus and sympathetic nerves in the neck and thorax which ranks as one of the best anatomical plates that have been produced to date (Fig. 3). Examination of this plate shows the high degree of perfection



Fig. 3. Neubauer's plate of the cervical sympathetic and vagus nerves.

This superb engraving gives as accurate a picture of the innervation of the heart as any modern illustration prior to the discovery of the thoracic cardiac nerves in 1927 (compare with Fig 14). (From *Descriptio anatomica nervorum cardiacorum*, Frankfurt, 1772.)

which had been reached by the gross anatomists at the end of the eighteenth century.*

As in other fields of medical science, anatomical knowledge developed far ahead of physiological experiment, but after Harvey's work on the circulation of the blood, investigation of function by experiment began. Willis sectioned both vagus nerves in the dog and reported that there ensued "great trembling" of the heart. In 1669 Lower, one of his pupils, published the earliest observations on stimulation of the vagus. Further experiments by Ens (1745) and by the Webers (1846) a century later finally established the role of the vagus in inhibition of the heart. The discovery that the sympathetic trunks originate below the cranium and not from the brain stem, as described by Galen and all subsequent anatomists, was worked out by François-Pourfour du Petit in 1727. He was likewise the first to observe the pupillary paralysis which follows cervical sympathectomy, thus antedating Claude Bernard and Horner by over a hundred years.

The first appreciation of involuntary movements and visceral sensation developed out of the experiments of Whytt (1751). This man, who is little known in medical history, is really an outstanding figure. He was the first to gain an insight into such fundamental concepts as the tone of skeletal muscle, the reflex responses of the pupils to light, and the fact that "the distension of hollow muscle has a remarkable influence towards exciting them into action." Whytt's careful reasoning based on experiment first deflected the stream of medical thought away from the Galenic tradition of animal spirits and the theory that involuntary motion was dependent on the cerebellum. The ultimate expression of this theory had been reached in the writing of Willis, i.e., that "sympathy" was due to communications of the nerve tubes which issued from the cerebellum and the brain stem, more especially those belonging to the "eighth pair" (the tenth in present terminology) and the "intercostal nerve." Whytt (1765) revised this traditional view by stating that "sympathy" presupposed feeling and must therefore be dependent on nerves. Moreover, he drew the important deduction from his observations that nerve fibers were single units rather than anastomosing channels and that their activity was mediated through the brain and spinal cord. In the following quotation he gave not only the first suggestion of the neuron theory but also of reflex action: "Since every individual nerve appears to be quite distinct from every other, not only in its rise from the medullary substance of the brain or spinal marrow, but also in

* The nerve supply of the heart was also magnificently illustrated in the pen drawings of Antonio Scarpa in his *Tabulae neurologicae* (Pavia, 1795), with copper plates of Scarpa's drawings executed by Faustino Anderloni.

its progress to that part where it terminates, it follows, that the various instances of sympathy, observed between the different parts of the body, cannot be owing to any communication or anastomosis of their nerves. . . . If, therefore, the various instances of sympathy cannot be accounted for from any union or anastomosis of the nerves, in their way from the brain to the several organs; and if there are many remarkable instances of consent between parts whose nerves have no connection at all; it follows that all sympathy must be referred to the brain itself and spinal marrow, the source of all the nerves."

A more famous eighteenth-century physiologist, but one whose deductions concerning the nervous system were less accurate, was Albrecht von Haller. In his treatise on sensation and irritability von Haller (1760) attributed sensibility to nerves but postulated that irritability (contractility) was an independent function of muscle. He thereby delayed the development of the theory of reflex action already suggested by Whytt. Although von Haller discovered the sensibility of the parietal peritoneum, pleura, and pericardium to mechanical stimulation by experimentation, he believed that the apparent lack of sensation in the viscera was due to lack of nerve supply. Whytt, with his keener insight, had already suggested the idea of the "adequate stimulus." These two men were the first to make experimental studies on visceral sensibility.

In 1776 John Hunter, the great English anatomist, made the following observations: "If it is asked why the involuntary parts have nerves at all, the answer may be given that it is not for their common actions, but to keep up the connection between the whole, for without them an animal would become two distinct machines, and one might be acting very contradictorily to the other, but by the intercourse between will and voluntary parts, between the voluntary and involuntary, and also between these last and the mind, an universal and uniform agreement or regulation is kept up, which communication produces one kind of sympathy." Hunter furthermore noted "that in joy or anger the heart beats quick or slow according to those states; sickness may be produced, purging, and contraction of the bladder." He also felt that in digestion the action of the stomach was controlled by the sympathetic nerves rather than by the cerebral masses.

In the first half of the nineteenth century, work on the autonomic nervous system was pursued with increasing activity in France and Germany. The impetus for this was given by Xavier Bichat (*1800*, *1801*, and *1802*), a brilliant anatomist and physiologist who died in 1802 at the age of thirty-one. He pointed out that the nervous system regulated *"la vie organique"* and *"la vie animale,"* viz., its visceral and somatic functions in modern

terminology, but he made the error of thinking that this integration took place in the ganglia and not through the spinal cord. Bichat anticipated Cannon's ideas of homeostasis by observing the effect of the "will" over animal life and the effect of emotion on the circulation, respiration, digestion, and the secretory glands. He also originated the ideas which have recently been stressed by Crile (1938*A* and *B*), calling attention to the inferior evolution of the brain in many of the lower animals in comparison with the extensive development of the sympathetic plexuses. Bichat referred to the autonomic nervous system as the *"système des ganglions"* and not as the "vegetative nervous system." Credit for this term, commonly attributed to him, should be given to his pupil Reil (1807).

Although earlier workers had recognized that the viscera were not under voluntary control of the nervous system, they had not observed the structural differences between skeletal muscle and the muscular coats of the hollow viscera. This discovery was made by Johannes Müller (1840). Even he did not recognize that arteries possess a true muscular coat. The histological description of the muscular layer in the media was given by von Kölliker (1849) and its innervation by a periarterial sympathetic plexus by Henle (1868).

The great work of Claude Bernard began with his studies on the influence of the nervous system on the regulation of chemical activity in the tissues. It seemed probable to Bernard that chemical changes between the blood and tissues could affect local temperature, and he therefore began to investigate the action of the sympathetic nerves in the control of circulation. In March, 1852, he described the increase in temperature which develops in the side of the head following section of the cervical sympathetic trunk. The corollary phenomenon, that stimulation of the trunk produces vasoconstriction, was published in Philadelphia by Brown-Séquard the following August. The discovery of the vasodilator nerves arose from Ludwig's observations in the preceding year that stimulation of the chorda tympani nerve increased the flow of blood through the submaxillary gland. The vasodilator effect of stimulating the posterior spinal roots was observed by S. Stricker (1877*A*).

Bernard, in his work on the nervous regulation of the blood vessels, was interested primarily in the effect on tissue metabolism. This developed into his classic conclusion that the animal body became independent of its surroundings only after developing a mechanism for maintaining constancy of what he designated *"le milieu intérieur"* (the internal environment). Under this category he included control of body fluids—blood, lymph, cerebrospinal fluid, etc. He first pointed out the remarkable constancy in

the composition of the body fluids, and he inferred that the adjustments which regulate this delicate balance were carried out by the nervous system (1878). In Bernard's own words: "The stability of the *milieu intérieur* is the primary condition for freedom and independence of existence; the mechanism which allows for this is that which ensures in the *milieu interieur* the maintenance of all the conditions necessary to the life of the elements. . . . These are the same conditions as are necessary for life in simple organisms; but in the perfected animal, whose existence is independent, the nervous system is called upon to regulate the harmony which exists between all these conditions."

One other important contribution of Bernard was the overthrow of Bichat's theory of the complete independence of the ganglionic nervous system. According to Bichat, visceral reflexes were mediated outside the spinal cord through the peripheral ganglia. Bernard controverted this and stated that these reflex arcs run through the spinal cord. In this connection he made the statement that "the existence of centripetal sensory fibers must be admitted in the sympathetic as well as in the cerebrospinal system."

The detailed anatomy of the autonomic nervous system was explored with the improvement of the microscope and the introduction of the microtome by His in 1870. Ehrenberg, in 1833, gave the first accurate account of cell bodies in the sympathetic ganglia, and Valentin three years later described the typical internal structure of these cells, in addition to noting the difference between gray and white rami communicantes. Two years later Remak found that the sympathetic ganglion cells give off the unmyelinated nerve fibers, but it was a number of years before his views were accepted. Remak (1854), as recorded by Sheehan, described the sympathetic rami as follows: * "The lower branch ('ramus communicans sympatheticus s. revehens') was *gray* and soft in texture and contained many fine myelinated and unmyelinated nerve fibers. The latter type arose from the cells in the sympathetic ganglia and were distributed peripherally along the spinal nerve. The upper branch ('ramus communicans spinalis s. advehens') was *white* and of firmer texture and contained myelinated fibers. It could be traced centrally into both the dorsal and the ventral spinal roots. Some of the fibers were thought to arise within the spinal cord and end in the sympathetic ganglion, occasionally passing through one ganglion as a white bundle to end in a ganglion lower or higher in the chain." Sheehan continues. "Although the difference in colour and texture between the gray and the white rami had been recognized for many years, Remak's

* Sheehan, D "Discovery of the autonomic nervous system." *Arch Neurol. Psychiat.*, 1936, 35: 1081–1115, courtesy of American Medical Association, Chicago.

account is one of the earliest clear descriptions. In spite of an observation by T. S. Beck (1846) that the cervical and sacral nerves possess only gray rami, there was still no thought of limitation of the white rami to the thoracic and the upper portions of the lumbar region. The rami communicantes were believed to have connections with both the dorsal and the ventral roots and possessed, therefore, both sensory and motor functions. The muscles innervated were nonstriated and gave rise to 'involuntary' motion."

From the preceding paragraphs it is evident that a great deal was known about the basic structure of the vegetative nervous system by the middle of the nineteenth century. While a hint of its two component divisions had been reached in Claude Bernard's (1858*A* and *B*) classical experiments on the changes in blood flow through the submaxillary gland following stimulation of the sympathetic and chorda tympani nerves, no clear appreciation had been reached of the function of the vagus nerve. Its cardioinhibitory effect had been demonstrated by the Webers in 1846, but it was still not considered as a part of the ganglionic nervous system. Further confusion existed as to the role of the intracranial ganglia, viz., the ciliary ganglion, which had been described by Willis in 1683; the sphenopalatine and submaxillary ganglia, described by Meckel (1749) and discovered separately by F. Arnold (1827) and Brachet (1842); and the otic ganglion. In addition to these structures within the skull, the submucous and myenteric plexuses of the intestines had been described by Meissner in 1857 and by Auerbach in 1864.

The final discovery of the antagonistic action of the two component divisions of the autonomic system was made by Gaskell and Langley. The work of these brilliant investigators left few extensive gaps in the anatomical and physiological understanding of the autonomic system and opened the field of treatment of visceral disease to the surgeon.

Gaskell (1886) studied the formation of the peripheral autonomic plexuses and described the three divisions of finely myelinated neurons which are given off from the neural axis in its cranial, thoracolumbar, and sacral levels. From a study of these structures he observed that "each nerve fibre leaves the central nervous system as a fine medullated nerve fibre which passes directly into its appropriate ganglion, and there in consequence of communication with one or more of the ganglion cells loses its medulla and passes out not as a single non-medullated fibre but as a group of non-medullated fibres. Such ganglion cells . . . assist in the conversion of a single nerve fibre into a group of fibres."

As a result of these observations Gaskell (1916) formulated the term "involuntary nervous system" and defined it as a "system of motor nerve

the composition of the body fluids, and he inferred that the adjustments which regulate this delicate balance were carried out by the nervous system (1878). In Bernard's own words: "The stability of the *milieu intérieur* is the primary condition for freedom and independence of existence; the mechanism which allows for this is that which ensures in the *milieu intérieur* the maintenance of all the conditions necessary to the life of the elements. . . . These are the same conditions as are necessary for life in simple organisms, but in the perfected animal, whose existence is independent, the nervous system is called upon to regulate the harmony which exists between all these conditions."

One other important contribution of Bernard was the overthrow of Bichat's theory of the complete independence of the ganglionic nervous system. According to Bichat, visceral reflexes were mediated outside the spinal cord through the peripheral ganglia. Bernard controverted this and stated that these reflex arcs run through the spinal cord. In this connection he made the statement that "the existence of centripetal sensory fibers must be admitted in the sympathetic as well as in the cerebrospinal system."

The detailed anatomy of the autonomic nervous system was explored with the improvement of the microscope and the introduction of the microtome by His in 1870. Ehrenberg, in 1833, gave the first accurate account of cell bodies in the sympathetic ganglia, and Valentin three years later described the typical internal structure of these cells, in addition to noting the difference between gray and white rami communicantes. Two years later Remak found that the sympathetic ganglion cells give off the unmyelinated nerve fibers, but it was a number of years before his views were accepted. Remak (1854), as recorded by Sheehan, described the sympathetic rami as follows: * "The lower branch ('ramus communicans sympatheticus s. revehens') was *gray* and soft in texture and contained many fine myelinated and unmyelinated nerve fibers. The latter type arose from the cells in the sympathetic ganglia and were distributed peripherally along the spinal nerve The upper branch ('ramus communicans spinalis s. advehens') was *white* and of firmer texture and contained myelinated fibers. It could be traced centrally into both the dorsal and the ventral spinal roots. Some of the fibers were thought to arise within the spinal cord and end in the sympathetic ganglion, occasionally passing through one ganglion as a white bundle to end in a ganglion lower or higher in the chain." Sheehan continues: "Although the difference in colour and texture between the gray and the white rami had been recognized for many years, Remak's

* Sheehan, D "Discovery of the autonomic nervous system" *Arch Neurol. Psychiat.*, 1936, 35: 1081–1115, courtesy of American Medical Association, Chicago.

sacral portions of the neural axis, and he named this the "parasympathetic" division.

It should be observed at this point that although Langley primarily investigated the motor innervation of the viscera, he also (1903) observed large medullated axons in the peripheral autonomic plexuses which he described as sensory fibers because of their resemblance to ordinary sensory fibers in cutaneous nerves.* He believed that they passed through the ganglia without interruption and that they arose from the posterior sensory root ganglia.

More recent work of great pharmacological and clinical importance has been done following Loewi's fundamental discovery in 1921 that the parasympathetic nerve impulse is actually propagated to smooth muscle cells by a chemical mediator which resembles acetylcholine. In the same year Cannon and Uridil observed that the totally denervated heart can be accelerated on stimulation of the nerves to the liver, and ten years later Cannon and Bacq (1931) furnished proof that there is a sympathomimetic hormone produced by sympathetic action on smooth muscle which they named *sympathin*. Space does not permit an account of the methods which led to present knowledge of chemical mediation, but much of this which has a bearing on surgical problems is reviewed in Chapter V.

In recent years Cannon has completed the work begun by Claude Bernard, developing the role of the autonomic system in adapting the organism to shifting environmental and psychic changes. Readers who are interested in this field should refer to his monograph, *The Wisdom of the Body,* which gives a summary of his investigations and an excellent exposition of his deductions on the maintenance of "homeostasis." During his later years, in collaboration with Rosenblueth and other younger associates, Cannon explored the chemical mediation of the autonomic discharge by adrenine, sympathin, and acetylcholine, pointing out the increased sensitivity of smooth muscle after denervation. These studies have been incorporated in a recent monograph with Rosenblueth (1949) published after Professor Cannon's death.

The brilliant work of Gaskell and Langley on the peripheral autonomic plexuses has been carried upward into the brain, where investigation of the effects of stimulation of the hypothalamus, begun by Karplus and Kreidl in 1909, and of destruction of the nuclear masses by Ranson and his col-

* These large medullated axis cylinders had been observed by Gaskell (1886) and illustrated in Plate II, Figs. 8 and 9. Edgeworth (1892) later studied these fibers, at Gaskell's suggestion, and concluded that they carried visceral sensation.

cells to involuntary structures." Sheehan (1936) has credited Gaskell with being the first to recognize the existence of two antagonistic systems of nerves for the control of involuntary musculature and glandular secretion, one excitatory and the other inhibitory. In 1886 Gaskell wrote: * "The evidence is becoming daily stronger that every tissue is innervated by two sets of nerve fibres of opposite characters so that I look forward hopefully to the time when the whole nervous system shall be mapped out into two great districts of which the function of one is katabolic, of the other anabolic." In view of Langley's work which followed, this was a prophetic statement.

Langley's final establishment of the two great divisions of the involuntary nerves depended on Hirschmann's discovery in 1863 that moderate doses of nicotine prevent pupillary dilatation when the cervical sympathetic trunk is stimulated. In experiments with Dickinson in 1889, Langley found that nicotine acts by paralyzing the synapses between the preganglionic and postganglionic neurons in the sympathetic ganglia, and that, in the case of the nerves which dilate the pupil and constrict the vessels to the ear, these junctions are situated in the superior cervical ganglion. Following out this line of investigation, Langley was able to map out the position of the cell stations and distribution of most of the "preganglionic" and "postganglionic" neurons, which he so named in 1893. In 1898 he proposed the name "autonomic nervous system" to include the cranial, thoracolumbar, and sacral pathways. Since he was unable to prove that the cells of the Meissner and Auerbach plexuses were a part of the bulbar and sacral pathways, he referred to them in a separate category as the "enteric nervous system."

The functional distinction between the thoracolumbar and craniosacral divisions of the autonomic system followed the discovery of epinephrine, which was made by Oliver and Schäfer in 1895. The similarity between the action of epinephrine and stimulation of the thoracolumbar fibers, and also the phenomenon of the exaggerated response to the drug after ganglionectomy, were described by Langley in 1901*B* and also by Elliott (1905). This functionally and anatomically distinct portion of the autonomic outflow was designated the "sympathetic" Subsequently Langley (1905) found that pilocarpine and other drugs act in a similar way on structures innervated by the finely myelinated fibers which originate from the cranial and

* Gaskell, W H. "On the structure, distribution and function of the nerves which innervate the visceral and vascular systems." *J. Physiol*, 1886, 7: 1–80, courtesy of Cambridge University Press, Cambridge, England.

In 1913 Leriche called attention to the effect of periarterial sympathectomy in increasing the flow of blood to the extremities. J. I. Hunter (1924) and Royle (1924*A*) later advocated sectioning the sympathetic rami for the reduction of excessive muscle tone in spastic paralysis. Although this treatment was never generally accepted, its by-products have proved to be of extraordinary value. After these operations they noted that coincident vasomotor paralysis caused a striking increase in the circulation to the extremities. This observation led to the present surgical treatment of Raynaud's disease and other types of vasomotor spasm by sympathetic ganglionectomy. Leriche's publications and the visit of Hunter and Royle to this country in 1924 have been largely responsible for the stimulation of American investigation in the surgical problems of the sympathetic nervous system.

The reader who is interested in gaining further information about the growth of the present-day understanding of the autonomic nervous system should consult the historical paper published by Sheehan (1936). This contains a wealth of interesting data and an extensive bibliography. The author and the editors of the *Archives of Neurology and Psychiatry* have very kindly permitted us to quote numerous passages and to reproduce two of the figures. This article has been of inestimable value to us in preparing this chapter, and we wish to express to Professor Sheehan our appreciation and gratitude.

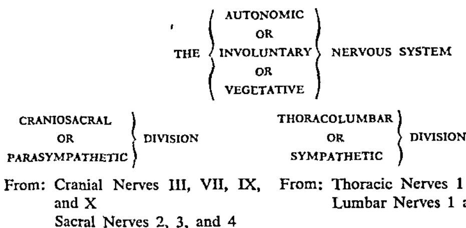
leagues (1939), has located the central autonomic ganglia in the diencephalon. An insight into the superimposed function of the cerebral cortex and its inhibitory effect on the lower centers has been obtained from Goltz's (1892) early experiments on the decorticate dog. He was the first to observe that, after removal of the cortex, animals develop manifestations of rage with evidence of intense activity of the sympathetic nervous system. Nothing further need be said in this historical outline concerning the development of anatomy, physiology, and other aspects of laboratory investigation. The present conception of these fundamental subjects is described in Part I, and their clinical importance, which is so closely interwoven with the neurosurgical treatment of cardiovascular and visceral disease, is further discussed in Part II.

To complete the historical background, it is only necessary to discuss the beginning of surgical intervention. W. Alexander (1889) of Liverpool appears to have been the first surgeon to operate on the sympathetic nervous system. He performed cervical sympathectomy for epilepsy. The Roumanian surgeon Jonnesco (1896) later tried this operation on a large series of epileptics. Jaboulay (1899*A*) of Lyons resected the lower cervical sympathetic chain for exophthalmic goiter. None of these procedures was strikingly successful, and, as a result, surgical interest in the sympathetic nervous system temporarily died away.

The first successful clinical application of sympathectomy was based on the work of François-Franck (1899). In this he stated that: * "The entire sympathetic system is endowed with direct sensory fibers and carries centripetal fibers from the heart and aorta to the cord and the brain stem. It seems logical to assume that sympathectomy acts as much in suppressing abnormal afferent impulses to the higher centers as in blocking efferent stimuli to the thyroid and heart. This new idea of aortic pain carried by the cervicothoracic sympathetic nerves suggests the thought of trying their resection in angina pectoris." An interval of many years elapsed before Jonnesco (1920) began to put these ideas to a test. His first case, in 1916, was brilliantly successful and was the beginning of modern operations on the cardiac nerves for the relief of angina pectoris. Particular credit is due to Professor René Leriche of the Collège de France for his continued emphasis on the efficacy of sympathectomy in the relief of various forms of visceral and vascular pain, which he has summarized in his monograph, *La Chirurgie de la Douleur* (1949).

* François-Franck, C. A "Signification physiologique de la résection du sympathique dans la maladie de Basedow, l'épilepsie, l'idiotie et le glaucome." *Bull. Acad. Méd Paris,* 1899, 41: 565–594, courtesy of Masson & Cie, Paris.

pharmacologically, as well as anatomically, the sympathetic and parasympathetic systems are very different. These differences were pointed out by both Gaskell (1916) and Langley (1921) and have been more completely developed in the work of Cannon (1929*A*). It is necessary to bring out the essential points of this classification here, although the anatomical and physiological differences must be discussed and amplified in the separate chapters which follow. For the purpose of greater clarity this may be set down in the following form:



II. Embryological Development

It is not within the scope of this surgical monograph to delve deeply into the embryology of the autonomic nervous system. This aspect is taken up with great thoroughness in Kuntz's textbook (1945). A simple exposition, however, is necessary for a basic understanding of the functions of these nerves.

In studying the growth of the nervous system in the human fetus, embryologists have shown the close relationship between the sympathetic and the spinal nerves. The primordial anlagen of the former appear early in embryonic development and are composed of cells which migrate peripherally from the neural tube (D. S. Jones, 1941). Froriep (1908) traced these cells from the primitive neural tube into the sympathetic trunks via the ventral nerve roots (Fig. 4). Kuntz (1945) has succeeded in tracing cells from these trunks into primordia of the celiac and other prevertebral plexuses of the abdominal viscera in the 6-mm human embryo. The development of the adrenal medulla also takes place by a migration of cells from the neural canal (Fig. 5). Chromaffin tissue thus represents a special differentiation of the terminal sympathetic neuron cell (cf. p. 49).

The vagus nerves likewise develop by cells migrating out from the midbrain (D. S. Jones, 1942). Cells identical with those in the ganglionic

CHAPTER III

Anatomy of the Autonomic Nervous System

In a monograph devoted to the surgical aspects of the autonomic nervous system, space prevents discussing the finer anatomical and embryological details. In this chapter, therefore, it has seemed best to take up the fundamental arrangement of the system as a whole, and to discuss its terminal ramifications mainly from the viewpoint of their possible interest to the surgeon. More will be said concerning regional anatomy in later chapters on surgical technique and the innervation of individual organs such as the heart. The best gross anatomical descriptions of the peripheral autonomic plexuses are to be found in the monographs of Hovelacque (1927) and of Delmas and Laux (1933) and in numerous papers by G A. G. Mitchell (1935*A* and *B*, 1938*A* and *B*, 1940, 1947, 1950). For a detailed neurohistological study, the reader is referred to Ranson's textbook (1947) or to Kuntz's extensive monograph on the autonomic nervous system (1945), its newest abridged version (1949), and also to the German texts of L. R. Müller (1931) and Stöhr's *Microscopic Anatomy of the Vegetative Nervous System* (1928). The Spanish *Sistema Neurovegetativo* of Pi Suñer (1947) is a valuable reference source, particularly to French, Spanish, and South American publications.

I. *Terminology*

At the very beginning of this chapter it is important to define the general terminology which will be used. Gaskell and Langley classified the autonomic nervous system into two main anatomical and functional divisions: the sympathetic or thoracolumbar outflow, which leaves the spinal cord over its anterior roots between the first thoracic and second lumbar segments; and the parasympathetic or craniosacral division. The vagus carries the major portion of the cranial parasympathetic axons, but similar fibers also run in the oculomotor, facial, and glossopharyngeal nerves. The sacral parasympathetic outflow leaves the spinal cord with the second, third, and fourth sacral nerves in the cauda equina. Physiologically and

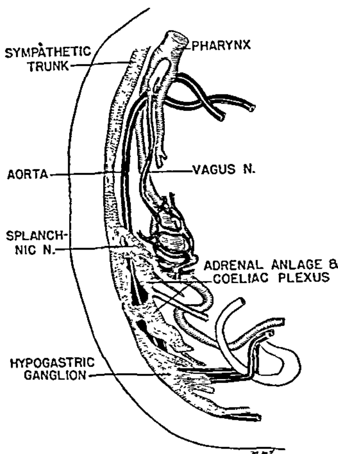


Fig. 5. Development of the adrenal glands and celiac plexus, 10 5-mm human embryo. (Redrawn from Brüning, F., and Stahl, O. *Die Chirurgie des vegetativen Nervensystems,* Julius Springer, Berlin, 1924.)

III. Anatomy of the Cranial Autonomic Centers

Cortical Representation of the Autonomic Nervous System. Control of the autonomic system from the highest level in the cerebral cortex is now well established (see Association for Research in Nervous and Mental Disease, 1948) This is concentrated in the frontal lobes. The cells from which the highest motor neurons arise have been found by Hoff and Green (1936) and Green and Hoff (1937) in monkeys to lie in the premotor cortex as well as at scattered points in the motor area. Thanks to current interest in lobotomy, a great deal has been learned about autonomic responses from other portions of the frontal cortex. These findings have been brought up to date in Fulton's (1949) review. Evidence from cortical stimulation carried out on the higher monkeys or in the course of frontal leukotomy and topectomy have shown clear-cut responses from areas 24 and 13 (the anterior limbic portion of the cingulate and the posterior orbital gyri). These are described in the following chapter.

cell clusters are present in abundance in the distal parts of the growing vagi. According to Kuntz (1909), the vagus forms the cardiac, pulmonary, and esophageal plexuses, whose primordia are already visible in the 8-mm embryo, whereas cells migrating out from the thoracolumbar

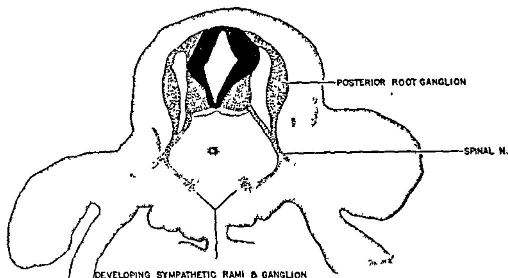


Fig. 4. Embryological development of sympathetic ganglia.
Transverse section through the thoracic region of a 7-mm human embryo. (Modified from Kuntz, A *The autonomic nervous system*, 3rd ed, Lea and Febiger, Philadelphia, 1945.)

segments of the spinal cord lay down the gastrointestinal and pelvic plexuses. At a later stage of embryonic development, outgrowing neurons of the opposite system invade each of these peripheral plexuses and thereby complete the characteristic dual innervation. Considerably less is known about the development of the autonomic ganglia in the head. According to Cowgill and Windle (1942), the primordia of the ciliary, sphenopalatine, otic, submaxillary and sublingual ganglia all arise from the neuroblasts which migrate along nerve fascicles of the trigeminal, facial, and glossopharyngeal nerves during 6- to 60-mm stages of embryonic growth.

The autonomic system, therefore, in both its cranial and thoracolumbar divisions, is developed from migrating cells which leave the brain stem and spinal cord in the early stages of embryonic development. These cells continue to divide by mitosis and thus form the peripheral visceral plexuses. Consequently, there is no fundamental difference between the autonomic and the cerebrospinal neurons.

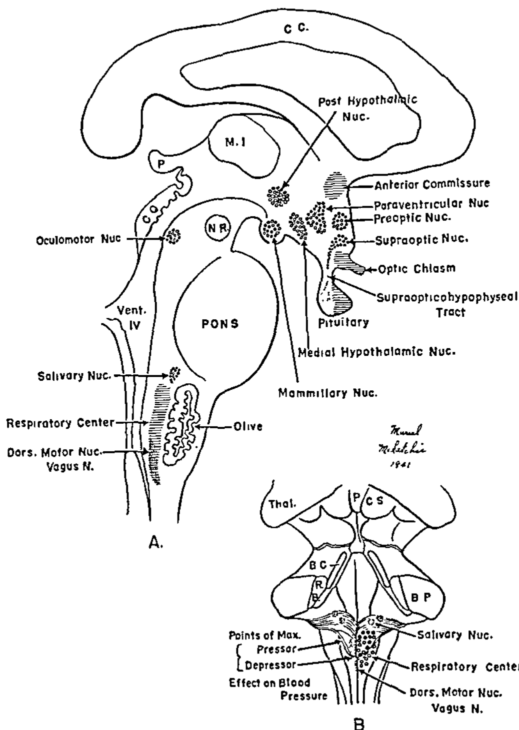


Fig. 6. Important nuclear areas and centers for autonomic activity in the brain stem.

A is the mid-line sagittal section, B is the dorsal view of medulla oblongata.

B C. Brachium conjunctivum	M.I. Massa intermedia
B.P. Brachium pontis	Thal. Thalamus
C.C. Corpus callosum	N.R. Nucleus rubor
C Q Corpora quadrigemina	P. Pineal
C.S. Colliculus superior	R.B. Restiform body

(These figures are based on the work of Ranson and Billingsley, 1916*B;* Clark, *et al*, 1938. Pitts, Magoun, and Ranson, 1939*B*. Ranson, 1947.)

After bilateral injuries to the rhinencephalon or the medial orbital gyri (area 14) in cats and monkeys, Bard and Mountcastle (1948) observed the phenomenon of sham rage. This comes from release of the hypothalamic centers that are normally governed by the olfactory area. Although nothing comparable to sham rage has been observed in man in the course of various procedures on the orbital surface of the frontal lobe, nor any lasting autonomic manifestations, Fulton wisely recommends that the prechiasmal region be spared.

The Autonomic Centers in the Diencephalon (Hypothalamus). Localization of autonomic control becomes much more apparent in the diencephalon, and increasingly distinct in the medulla and spinal cord. The cerebellum, on the other hand, plays only a minor part in autonomic regulation (see p. 65). Outstanding anatomical studies on the nuclei in the human hypothalamus, which have been shown to co-ordinate visceral activity and, to a large extent, to integrate the autonomic responses commonly associated with emotional expression, have been carried out by W. E. LeG. Clark and others (1938). This work has been summarized by Rioch, Wislocki, and O'Leary (1940). Phylogenetically, there has been little change in this ancient group of nuclear masses, and a certain fundamental ground plan is constant throughout the mammalian series (Grünthal, 1933). Clark lists sixteen nuclear areas in the human hypothalamus. The most important of these are the (1) preoptic, (2) supraoptic, (3) paraventricular, (4) posterior hypothalamic, (5) ventromedial hypothalamic, (6) dorsomedial hypothalamic, and (7) mammillary hypothalamic. The position of some of these is shown in Figure 6 A.

The fundamental significance of all these structures is by no means clear, but there is evidence to support Beattie's (1935) suggestion that the preoptic nuclei are concerned with parasympathetic functions, the paraventricular and more caudal group with the sympathetic, and the more laterally situated nuclear areas with both. In addition, the supraoptic nucleus gives rise to the supraopticohypophyseal tract and thereby regulates the secretion of the posterior lobe of the pituitary body. The action of the mammillary nuclei is uncertain Since lesions of the hypothalamus and its posterior projections, quite aside from damage to the supraopticohypothalamic tract and the pituitary mechanisms, lead to disturbances in regulation of the waking-sleep mechanism and alterations in energy exchange, the hypothalamus must be the level at which physical activity, heat loss, food intake, and body weight are integrated by the central nervous system. (For a more detailed discussion, see p. 65.)

Evidence confirming the existence of a similar pathway in man has been obtained by List and Peet (1939) from observation of alterations in sweat secretion in a series of lesions of the brain stem. Further confirmation of an uncrossed descending sympathetic pathway in the lateral portion of the medulla dorsal to the inferior olive comes from Duthie and Máckay's (1940) observations after thrombosis of the posterior-inferior cerebellar artery. These patients have vasodilatation of the cutaneous blood vessels and absence of sweating with added ptosis and myosis on the side of the lesion.

Studies made on human beings after unilateral injuries to the spinal cord and animal experiments made by stimulating the hypothalamic centers after similar experimentally produced lesions have given an insight into the descending autonomic pathways in the spinal cord. According to Harrison, Wang, and Berry (1939), hypothalamic impulses may descend in the spinal cord uncrossed, or they may cross in the brain stem or in the spinal cord below the cervical segments. It is also known that some functions are bilaterally represented (vasomotor), some entirely unilateral (pupillary dilators). In the thoracic cord these descending sympathetic axons finally establish synapses with sympathetic motor cells in the intermediolateral column. This column lies in the lateral horn of spinal gray matter and gives off the sympathetic axons to the peripheral ganglia (Fig. 7).

The visceral afferent fibers enter the spinal cord in the posterior roots. The upper sensory neuron cells are situated in the posterior horn of gray matter, and their axons cross in the anterior commissure to ascend in the spinothalamic and possibly other closely related pathways. There has been much disagreement concerning the transmission of visceral pain. Contrary to certain authorities who believe that pain from a unilateral organ like the gall bladder ascends in both anterolateral columns, it is our opinion that the pathway is entirely crossed and differs in no way from that subserving somatic structures. Evidence to support this point is given in Chapter VI. Discomfort from distention of the bladder and rectum as well as testicular compression is likely to persist after bilateral cordotomy; this is also the case after complete transections of the lower thoracic cord. These sensations may ascend in part in the extraspinal autonomic pathways and also in the posterior columns. Dr. R. S. Morison, while Associate in Anatomy at the Harvard Medical School, suggested to us the added possibility that these sensations may also run for considerable distances over the tracts of Lissauer. These tracts, which are composed of unmyelinated and finely myelinated fibers, run with, but are anatomically

Autonomic Centers in the Midbrain and Medulla. Anatomical studies show that autonomic regulation is transmitted to the peripheral plexuses through a series of nuclei in the midbrain, pons, and medulla. These lie close to the mid-line beneath the sylvian aqueduct and the floor of the fourth ventricle (Fig. 6 B). The pupillary constrictor center is an integral part of the oculomotor nucleus in the upper mesencephalon. At the junction of the pons and medulla, the salivary nucleus is located in the reticular formation between the facial nucleus and the nucleus ambiguus (Ranson, 1947). The dorsal motor nucleus of the vagus lies at the level of the latter structure, just beneath the floor of the fourth ventricle. Two particularly important reflex centers are situated in the medulla oblongata. These consist of the respiratory and vasomotor centers Both areas have been located with considerable accuracy The former lies in the ventral reticular formation immediately over the inferior olive (Pitts, Magoun, and Ranson, 1939*B*). The vasomotor center lies in the medulla as a strip along the floor of the fourth ventricle and runs from the facial colliculus to terminate a short distance rostral to the calamus scriptorius (Ranson and Billingsley, 1916*A*). It is closely associated with the dorsal motor nucleus of the vagus.

Autonomic Pathways in the Brain Stem and Spinal Cord. Anatomical knowledge of the descending pathways for impulses from the hypothalamic centers to the nuclei in the middle and hindbrain and to the spinal centers is far from complete. Degeneration studies following posterior hypothalamic lesions led Beattie, Brow, and Long (1930) to conclude that fibers descend in the periventricular gray matter, but failed to demarcate the course of the efferent axons in the spinal cord These fibers become more medially placed at lower levels and were traced directly to the spinal cord. Magoun (1940) has described more recent investigations which have been carried out in Ranson's laboratory with the technical advantage of direct stimulation of the hypothalamic areas and observations on the effect of circumscribed lesions in the brain stem and spinal cord. These experimental studies * "confirm the presence of some periventricular and medially situated connections descending from the hypothalamus, but indicate that of far greater importance is a pathway which runs backward from the lateral hypothalamic area through the tegmentum of the midbrain and pons, to traverse the lateral part of the reticular formation of the medulla, and descend in the ventrolateral column of the spinal cord. . . . This pathway is made up of both ipsilateral and crossed connections, with crossing occurring both in the brain stem and at spinal levels."

* Magoun, H. W. "Descending connections from the hypothalamus" *Res. Publ. Ass. nerv. ment Dis*, 1940, **20**: 270–285, courtesy of Williams and Wilkins, Baltimore.

IV. The Thoracolumbar Division

The Paravertebral Sympathetic Ganglia and Their Rami Communicantes. The paravertebral ganglionated chains run on either side of the vertebral column from the base of the skull to the ganglion impar at the coccyx (Fig. 8). The constituent ganglia are good-sized fibrous bodies and, together with their rami communicantes and the splanchnic nerves, constitute the only sympathetic structures which are seen by the casual student of anatomy. Throughout their length the chains are closely applied to the vertebral bodies, lying ventral to the transverse processes in the cervical spine, laterally over the heads of the ribs in the thorax, and on the anterolateral surfaces of the lumbar vertebrae. At the diaphragm they pass between the lateral and medial crura. The twelfth thoracic ganglion lies within the substance of the diaphragm. Here the chain is usually very attenuated and shifts from a lateral to a more anterior position at the first lumbar ganglion, where it lies just beneath the edge of the crus of the diaphragm. The lumbar ganglia lie on the anterior surfaces of the vertebral bodies at the attachment of the psoas muscle and under the lateral edge of the vena cava and aorta. The fourth lumbar ganglia are usually located beneath the bifurcating common iliac arteries. There is rarely a fifth pair. The chains then descend in the hollow of the sacrum to fuse in front of the coccyx in the ganglion impar. In a few cadavers Pick and Sheehan (1946) have found double strands of the sympathetic trunk, but never over greater lengths than between two contiguous ganglia. Cross connections between the right and left ganglionic chains are fortunately never of clinical importance. Kuntz (1949), in his monograph on *The Neuroanatomic Basis of Surgery of the Autonomic Nervous System,* has given a particularly useful presentation of the gross and microscopic anatomy of the ganglia and their rami. Although abnormal histological findings in these structures are common in adults, they are found just as frequently in normal individuals as in those suffering from hypertension, Raynaud's disease, etc. Bergmann, Harman, Pick, and Wertheim (1948) have described these changes and summarized the literature on this subject.

In the neck, a condensation has occurred, there being only three or four ganglia for the eight cervical nerves (Fig. 9). While the average ganglion in the sympathetic trunk measures about 3 to 5 mm in length, the superior cervical and stellate ganglia are much larger. The former is a long fusiform structure, running beneath the carotid sheath from the base of the skull 2 to 3 cm down into the neck. It is formed by a fusion of the ganglia connected with the three highest cervical nerves and sends gray rami to each of these.

quite distinct from, the posterior columns. Ranson and Billingsley (1916*B*) have suggested that they are an alternate pathway for pain and that there are connections between them and the spinothalamic tracts.

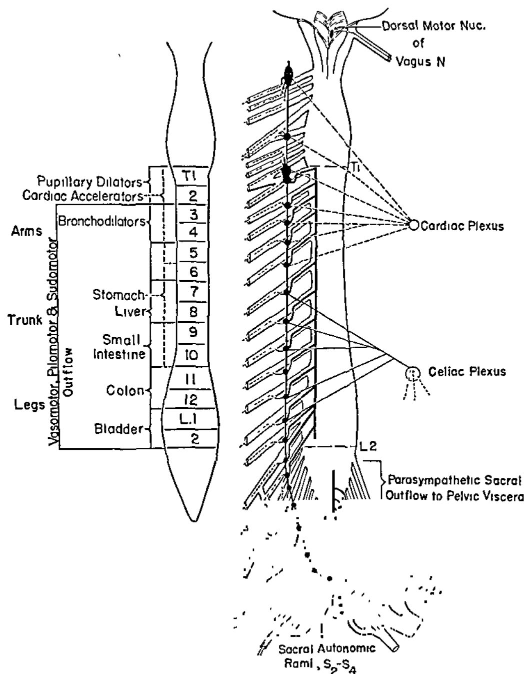


Fig. 7. The intermediolateral cell column and its segmental outflow of preganglionic axons

——— Preganglionic axon ‒ ‒ ‒ Postganglionic axon

Below the superior cervical ganglion the sympathetic trunk dwindles into a fine strand which runs on the deep fascia of the neck on the anterior surface of the longus capitis and longus colli muscles. In order to make certain of identifying the sympathetic trunk, the surgeon should bear

Fig. 9. The cervical sympathetic nerves.

in mind that the vagus runs within the fascia of the carotid sheath; when this structure is elevated on a retractor, the sympathetic trunk adheres to the underlying fascia. The trunk lies distinctly medial to the phrenic nerve, which originates from the third and fourth cervical nerves in this same plane. With an understanding of these facts, no other anatomical structure is likely to be confused with it.

The middle cervical ganglion, frequently absent, lies at the level of the

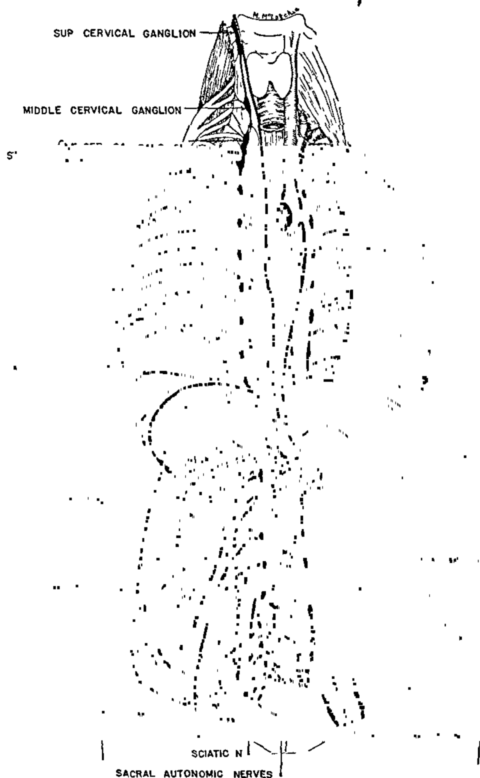


Fig. 8. The sympathetic ganglionated chains and prevertebral plexuses.

ganglion.* In addition to a small number of fibers of the somatic sensory type which will be discussed later, these white rami carry the so-called "preganglionic" axons. Their myelinated fibers originate in the intermediolateral cell column in the lateral horn of spinal gray matter, reach the spinal nerve over the anterior roots, and end in a sympathetic ganglion in synaptic relation (see below) with a number of postganglionic neuron cells.

In contrast to the white rami, which connect the lateral horn cells in the cord with the sympathetic ganglia, the gray rami carry outgoing unmyelinated axons to the peripheral structures. The trophic cells of these fibers are situated in the sympathetic ganglia, and their axons terminate in smooth muscle and glands throughout the body. In the case of the vasoconstrictor, sudomotor, and pilomotor fibers to the trunk and extremities, the postganglionic axons take origin in the paravertebral ganglionated chains and thence, through the gray communicant rami, rejoin the spinal nerves by which they are distributed to the periphery. In the case of the viscera the postganglionic neurons to the cardiac and pulmonary plexus also arise in the ganglia of the upper thoracic sympathetic chains. But the preganglionic fibers which make up the splanchnic, mesenteric, and hypogastric plexuses for the most part run through the paravertebral ganglia in continuity and end in the celiac, preaortic, and hypogastric ganglia. The postganglionic neurons which originate in these ganglia are therefore relatively short structures. This whole subject is ably presented in Kuntz's book (1949).

It is important to remember that there are no white rami in the cervical or lower lumbar segments. While some of the preganglionic axons end in the paravertebral ganglion to which a given white ramus leads or run through it into the splanchnic plexuses (Fig. 10), many others run either upward or downward over as many as three to six ganglia in the paravertebral chain (Langley, 1896). Eventually, each terminates in a ganglion in synaptic connection with a number of postganglionic neuron cells. Ranson and Billingsley (1918) have counted the number of axons in the cervical sympathetic trunk and also the cells in the superior cervical ganglion and thereby computed that each preganglionic axon synapses with some twenty-two postganglionic fibers. Similar counts made by Wolf (1941) gave ratios of 1:17 in one cat and 1:22 in another. *This is the reason for the diffuse nature of the sympathetic discharge.*

The diffuse distribution of preganglionic fibers in a single spinal root

* It is worth while pointing out that while the terms white and gray rami are appropriate from the angle of the neurohistologist in differentiating rami made up of axons that are largely myelinated or unmyelinated, the surgeon with either variety grasped on a nerve hook cannot distinguish between them. It is not even possible to identify these structures by their origin from the spinal nerves, as Pick and Sheehan have shown that the point of emergence of the white ramus is often distal to the gray.

sixth cervical vertebra behind the inferior thyroid artery. It is formed by a coalescence of the fourth and fifth cervical ganglia. There is also a second and more constant ganglion situated in the lower cervical chain medial to the origin of the vertebral artery. This has been called the intermediate ganglion by Jonnesco, Hovelacque, and Leriche. It is connected with the inferior cervical ganglion by two short fibers which encircle the vertebral artery, and also by the ansa subclavia or annulus of Vieussens.

The inferior cervical and first thoracic ganglia are usually fused into a single dumbbell-shaped structure known as the cervicothoracic or stellate ganglion. These paired ganglia may be completely fused, or they may appear as two quite separate structures. Usually, there is a distinct isthmus between the two halves, the upper component giving off rami to the three lowest cervical nerves, while the lower is connected to the first thoracic nerve by a large and a smaller ramus communicans. This important structure lies between the head of the first rib and the vertebral artery at its junction with the subclavian It often reaches a length of 2 cm. The remaining thoracic, lumbar, and sacral ganglia are much smaller and show frequent anatomical variations.

The most exact studies of the ganglionic chains have been made by Pick and Sheehan (1946). These anatomists emphasize the fact that, below the level of the first thoracic, the surgeon can never be sure of exactly which ganglion he is removing. This can only be ascertained with certainty by anatomical dissection and tracing the connections of the communicating rami with the spinal nerves. The lumbar ganglia in particular are difficult to identify, as such wide fusion may occur that the greater part of the lumbar chain consists of a single elongated ganglionic mass. There is every conceivable variation from a single ganglion to six lumbar ganglia, and the surgeon has no right to conclude that a ganglion on any given lumbar vertebra is necessarily connected with the corresponding spinal nerve. Yeager and Cowley (1948) have also emphasized this point.

The central and peripheral connections of the sympathetic ganglia are shown in Figure 10. While the normal sympathetic preganglionic outflow leaves the cord between the first thoracic and second lumbar segments, variations may take place if the brachial plexus is pre- or postfixed In the case of rostral shift the preganglionic outflow extends from C8 to L1, with a caudal shift from T2 to L3 Evidence for these variations has been summarized by Goetz (1948*B*). In the thoracic and upper lumbar segments of the cord each spinal nerve, on emerging from the intervertebral foramen, gives off a white ramus communicans to its corresponding sympathetic

glands, and presumably to the peripheral arteries as well, may by-pass the paravertebral ganglia. Small ganglia have been found in the cervical, upper thoracic, and lumbar segments by Wrete (1934 and 1943), Skoog (1947), Kuntz and Alexander (1950), and others (mentioned by Kuntz in his monograph, 1949), located at the origin of the sympathetic rami close to spinal nerves (Fig. 11). By the arrangement illustrated in Figure 11, it is

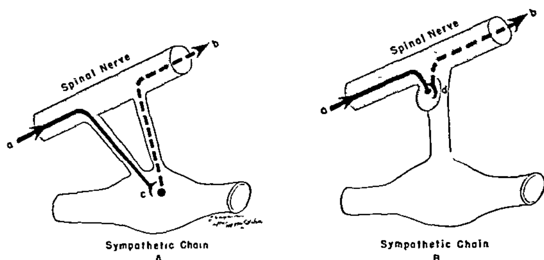


Fig. 11. Variations in the synaptic junction between pre- and postganglionic neurons

A. a = Preganglionic neuron
b = Postganglionic neuron
c = Synapse in paravertebral sympathetic ganglion

B. a = Preganglionic neuron
b = Postganglionic neuron
d = Synapse in intermediate ganglion outside paravertebral sympathetic chain (modified from Wrete, 1935)

possible for the preganglionic fibers to establish synaptic connections at these points with postganglionic neuron cells, whose axons promptly reenter the spinal nerve. In this way a few fibers may reach the periphery without ever entering the paravertebral chain. This doubtless accounts for the fact that, after extensive removals of the thoracolumbar ganglionated chains, residual sweating, especially in the region of the anterior thigh, has been commonly observed. Such accessory connections may also account for the incompleteness of sympathetic denervations after other procedures

The important principle that the axons in the white rami do not run directly to the structures which they innervate, but form synaptic connections with a second set of neurons in the paravertebral or prevertebral ganglia, was discovered by Langley (1900*B*). Langley showed that these synapses could be blocked by painting the ganglia with nicotine, although stimulation of the gray rami still produced an undiminished response. His work showed that there are at least three orders of neurons in the sympa-

is brought out by electrical stimulation. Stimulation of T4, for example, causes a pilomotor response extending from C5 to T6 dermatomes (Foerster, 1936). Ray *et al.* (1943) found that stimulation of any anterior root from T2 to T10 resulted in a simultaneous change in cutaneous resistance of all the fingers.

A recent anatomical discovery of importance to the surgeon is the fact that a certain number of sympathetic efferent fibers to the sweat

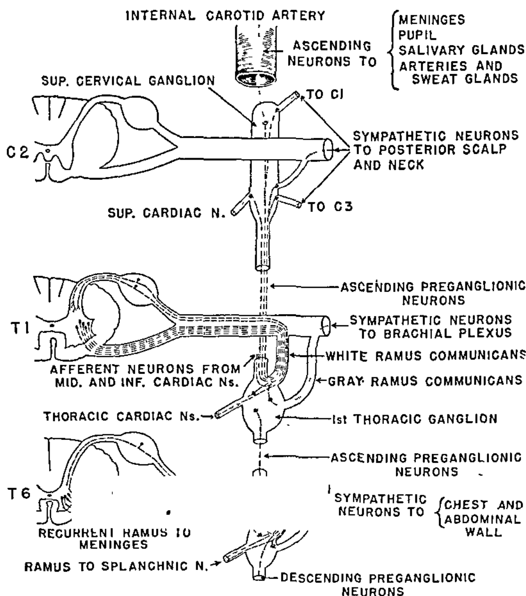


Fig. 10. Diagram of the peripheral visceral neurons
— — — Preganglionic motor neuron
.... Postganglionic motor neuron
–·–·– Viscerosensory neuron

many of these are doubtless concerned with the mediation of visceral reflexes, stimulation of the nerve in the course of operation under local anaesthesia has shown us its importance in the conduction of pain (see p. 133). From their work with the cathode-ray oscillograph, Gasser (1935) and also Heinbecker and Bishop (1935) concluded that different types of nerve fibers have varying rates of conduction. The most heavily myelinated variety, which are known to carry motor impulses to skeletal muscle, have the most rapid rate of conduction. These are not present in the autonomic nerve trunks. The less heavily myelinated, as well as a few unmyelinated axons with progressively slower rates of conduction, transmit sensory impulses, both somatic and visceral. A certain number of these are found in the vagus, as well as in the cardiac, splanchnic and hypogastric plexuses, *intermingled with a far greater number* of visceromotor fibers. Of the latter, the preganglionic axon is thinly myelinated, whereas the postganglionic is unmyelinated. From Ranson's (1947) description of the posterior roots, it is known that the larger and more rapidly conducting afferent fibers enter the posterior columns, whereas other axons with little or no myelinization enter Lissauer's tracts. These are pain fibers. Both types are present in the visceral nerves, the former presumably transmitting visceral reflexes and remaining for the most part below the threshold of consciousness. Physiologically as well as anatomically, there is probably no fundamental difference between the viscerosensory fibers in the cardiac, splanchnic, and hypogastric plexuses and those which reach the skin through somatic nerves.

While all the ganglia in the paravertebral sympathetic trunks give off gray rami of nearly uniform size to the spinal nerves, the size of their visceral rami varies greatly. Some, such as the network given off by the cervical ganglia to the carotid artery, the thoracic cardiac and aortic nerves, and the ureteral and ovarian plexuses, are made up of such fine filaments that they can only be demonstrated by a special microdissection technique (Wharton, 1932). Others constitute very definite structures. The most important of the larger visceral branches are the superior, middle, and inferior cardiac and the splanchnic nerves. The former are given off from the corresponding cervical ganglia (Fig. 9).

The major splanchnic nerve is made up of rami leaving the fifth * to the ninth ganglia of the thoracic paravertebral chain. It descends on the bodies of the lower thoracic vertebrae. There is often an enlargement,

* Additional higher rami, certainly as high as the fourth and rarely the third thoracic ganglia, may enter the *major splanchnic nerves* (G. A. G. Mitchell, 1947; Pick and Sheehan, 1946).

thetic motor pathway: the first running from the central ganglia in the diencephalon to the lateral horn in the cord, a second group of preganglionic fibers from the lateral horn to the sympathetic ganglia, and a third of postganglionic fibers from the ganglia to the arteries, glands, and various viscera.

Langley's conception of a chain of neurons interrupted by synapses has been questioned by Stöhr (1938 and 1939). This well-known German microscopical anatomist has rejected the neuron doctrine, as applied to the autonomic nervous system, and claimed that there is no interruption of the fiber pathways at the synapse. Sheehan (1941), however, has marshaled most convincing data against such a syncytial conception. This includes evidence from comparative anatomy (Woollard and Harpman, 1939) and observations of fiber degeneration by Kuntz (1940) and by Gibson (1940). More recently, Hillarp (1946), by more refined staining of the terminal fibers, found that the construction of the ganglionic pericellular apparatus is incompatible with the existence of a terminal reticulum.* "Within the ground plexus each axon has a certain extension, and innervates in its course a certain number of cells . . . the neuro-effector unit. . . . A neuro-effector unit is not innervated by one neuron alone, however, but several neurons converge towards it. . . . By the over-lap thus present . . . the response of the autonomic effector system on indirect stimulation may be modified both by temporal and by spatial summation effects." The objections raised by Stöhr against the neuron doctrine were evidently based on unreliable neurohistological methods.

In contrast with the peripheral autonomic nerves, which are broken up into preganglionic and postganglionic neurons, visceral afferent neurons differ in no way from afferent neurons in the somatic system. Their cells lie in the dorsal root ganglion (Fig. 10). Like the fibers that carry somatic pain, they establish central connections in the spinal cord with cells in the posterior horn. Their long peripheral fibers traverse the posterior roots and the white and gray communicant rami. Instead of being interrupted in the sympathetic ganglia, as is the case with the motor fibers, their axons run directly to the peripheral plexuses in the visceral nerves.

Proof of the presence of sensory axons in the sympathetic trunks has been derived from a study of the histological characteristics of the constituent fibers (Edgeworth, 1892; Langley, 1903) as well as from their electrical conduction rates Kuntz (1949) claims that the major splanchnic nerve contains a larger proportion of afferent than efferent fibers. While

* Hillarp, N. A. "Structure of the synapse and the peripheral innervation apparatus of the autonomic nervous system" *Acta Anat.*, 1946, Suppl. IV, courtesy of Hakan Ohlssons Boktryckeri, Lund, Sweden.

many of these are doubtless concerned with the mediation of visceral reflexes, stimulation of the nerve in the course of operation under local anaesthesia has shown us its importance in the conduction of pain (see p. 133). From their work with the cathode-ray oscillograph, Gasser (1935) and also Heinbecker and Bishop (1935) concluded that different types of nerve fibers have varying rates of conduction. The most heavily myelinated variety, which are known to carry motor impulses to skeletal muscle, have the most rapid rate of conduction. These are not present in the autonomic nerve trunks. The less heavily myelinated, as well as a few unmyelinated axons with progressively slower rates of conduction, transmit sensory impulses, both somatic and visceral. A certain number of these are found in the vagus, as well as in the cardiac, splanchnic and hypogastric plexuses, intermingled with a far greater number of visceromotor fibers. Of the latter, the preganglionic axon is thinly myelinated, whereas the postganglionic is unmyelinated. From Ranson's (1947) description of the posterior roots, it is known that the larger and more rapidly conducting afferent fibers enter the posterior columns, whereas other axons with little or no myelinization enter Lissauer's tracts. These are pain fibers. Both types are present in the visceral nerves, the former presumably transmitting visceral reflexes and remaining for the most part below the threshold of consciousness. Physiologically as well as anatomically, there is probably no fundamental difference between the viscerosensory fibers in the cardiac, splanchnic, and hypogastric plexuses and those which reach the skin through somatic nerves.

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the ganglion splanchnicum, situated just above the diaphragm. This contains postganglionic neuron cells which have not migrated as far distally as those in the celiac ganglion. The major splanchnic then penetrates the crus of the diaphragm and ends in the celiac or semilunar ganglion around the origin of the celiac axis from the aorta. The minor splanchnic nerve originates from the tenth and eleventh thoracic ganglia and penetrates the

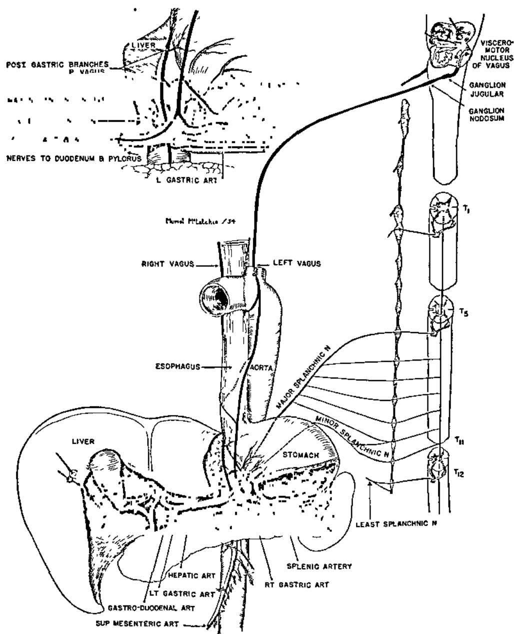


Fig. 12. The splanchnic and vagus nerves

The major splanchnic nerve may arise from higher segments (T4 or even T3). These and its variable descending rami to the aorta are not shown

diaphragm with the major trunk. It enters the aorticorenal ganglion and is concerned largely with innervating the adrenal. The twelfth thoracic ganglion gives off fibers to the least splanchnic nerve, which ends in the renal plexus (Fig. 12). Additional fibers are given off to the adrenal gland and kidney from the first and possibly from the second lumbar ganglia. A description of the distribution of their terminal plexuses is given on page 46.

V. The Craniosacral Division (Parasympathetic System)

The Vagus Nerve. The vagus is a mixed voluntary-involuntary nerve; its motor fibers to the pharynx and vocal cords, as well as its sensory fibers to the larynx, would appear to belong properly to the somatic system. Nevertheless, since the musculature in the pharynx and larynx have developed from the gill arches, the motor fibers, whose cell bodies lie in the nucleus ambiguus, have been classified as "*special* visceral efferent neurons" by American anatomists. This is in contradistinction to the "*general* visceral efferent neurons," which arise in the dorsal motor nucleus of the vagus and supply the heart, smooth muscle, and glands of the digestive tract. Below the larynx the greater portion of the vagal axons carry involuntary motor and afferent impulses to and from the thoracic and upper abdominal viscera. The nerve originates in the medulla oblongata from three groups of cells (Fig 13):

a. The nucleus ambiguus—voluntary innervation of the striated muscle in the pharynx and vocal cords.
b. Dorsal motor nucleus—concerned with visceral motor innervation.
c. Fasciculus solitarius—sensory innervation of pharynx and larynx through neurons whose cells lie in the ganglion jugulare; visceral afferent innervation through neurons whose cells lie in the ganglion nodosum.

The nerve leaves the skull through the jugular foramen, expanding at this point into the jugular ganglion and just below the foramen into the ganglion nodosum. The enlargements correspond to the dorsal root ganglia of the spinal nerves and contain the cells of the afferent neurons, the jugular containing the cells of somatic sensory fibers, the nodose ganglion those from visceral structures. At this level there are also many anastomoses with the glossopharyngeal and hypoglossal nerves, as well as numerous connections with the superior cervical sympathetic ganglion and the carotid sinus plexus. The course of the vagus in the carotid sheath and through the thorax is illustrated in Figure 14. The distribution of the vagi along the esophagus is subject to considerable variation and has become of major importance to surgeons owing to current interest in vagotomy for

the treatment of peptic ulcers. Excellent descriptions of the course of the nerve and its distribution to the thoracic and abdominal viscera have been published by Braeucker (1927), G. A. G. Mitchell (1938*A* and 1940), and Royster *et al.* (1949). In the thorax it establishes further connections

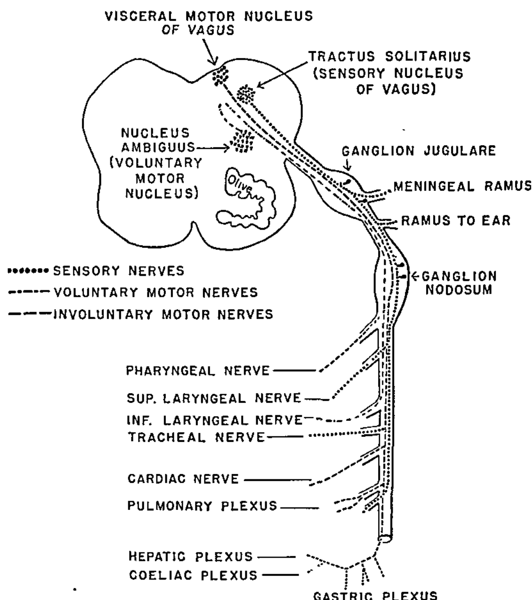


Fig. 13. Origins of vagus nerve (Modified from Bruning, F., and Stahl, O. *Die Chirurgie des vegetativen Nervensystems,* Julius Springer, Berlin, 1924.)

with the sympathetic through the inferior cervical ganglion and then enters into the formation of the cardiac, pulmonary, and esophageal plexuses. Below the diaphragm the left vagus sends branches along the lesser curva-

ture to the anterior wall of the stomach and a large ramus to the hepatic plexus (Fig. 12). The right vagus, which at this point lies behind the cardia, sends its fibers to the posterior wall of the stomach and through the celiac

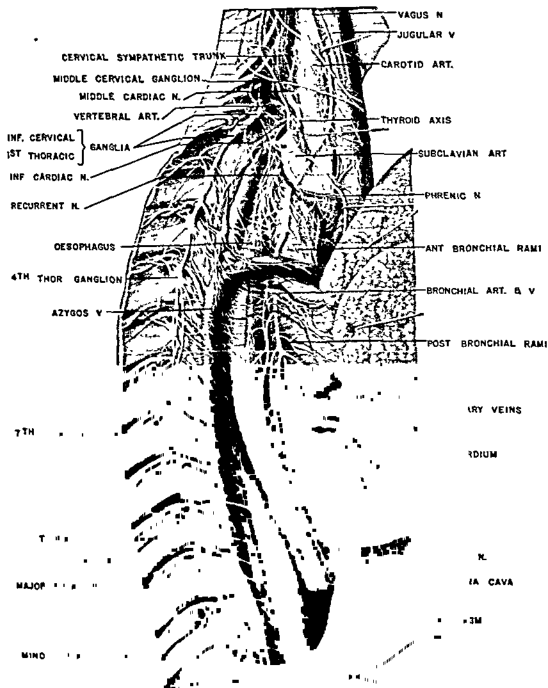


Fig. 14. Relations of the vagus and splanchnic nerves in the thorax. (Reproduced from Braeucker, W. "Der Brustteil des vegetativen Nervensystems und seine klinisch-chirurgische Bedeutung." *Beitr. Klin. Tuberk.*, 1927, 66: 1–65, courtesy of Julius Springer, Berlin.)

ganglion to the terminal plexuses in the upper abdominal viscera. Unlike the sympathetic, the preganglionic axons of the vagi run directly into the terminal plexuses in the walls of the viscera before forming synaptic connections with short, postganglionic fibers (Fig. 19). This arrangement results in a specific localized effect in contrast to the diffuse sympathetic discharge.

The Sacral Autonomic System. The sacral parasympathetic outflow leaves the spinal cord with the second to fourth sacral nerves in the cauda equina (Fig. 20). The pelvic rami (nervi erigentes) do not pass through the sacral sympathetic chains but run directly into the hypogastric ganglia and thence to the walls of the pelvic viscera. Their postganglionic neurons originate in the intrinsic plexuses of the genitalia, bladder, and rectum.

Other Parasympathetic Pathways. In addition to the vagus and sacral autonomic pathways, several lesser channels exist (Fig 15). Those of most importance to the surgeon are:

a. Pupillary-constrictor fibers.
b. Fibers to the lachrimal glands and nasal mucosa
c. Fibers to the salivary glands.

A final important anatomical principle is the mixed character of the autonomic nerves. The vagus carries sensory and motor fibers to the pharynx and larynx, as well as the cranial autonomic neurons. In the neck there are numerous anastomoses between it and the cervical ganglia. In all the visceral plexuses a further mixing of the two systems takes place. This is important from a surgical standpoint, because it makes it difficult to paralyze one system exclusively and to leave the other entirely intact.

VI. The Peripheral Autonomic Plexuses

Having taken up the formation of the cranial and sacral portions of the parasympathetic, as well as the thoracolumbar sympathetic system, it remains to show how these two distinct sets of fibers are combined to form the individual peripheral plexuses. As many of these have yet to be attacked surgically and as those which are of importance to the surgeon will be discussed in subsequent chapters, the most satisfactory way of describing their general make-up is by the briefest possible skeleton outline. This section is intended to serve only as a reference, and not to be read through in continuity.

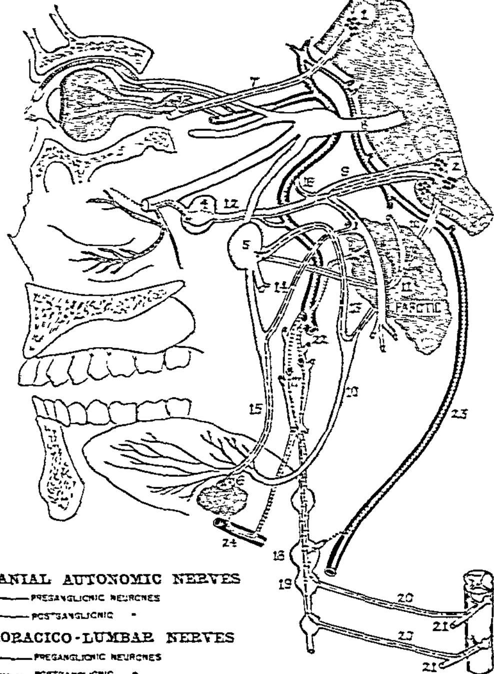


Fig. 15. The autonomic innervation of the head. (Modified from Hovelacque, A. *Anatomie des nerfs craniens et rachidiens et du système grand sympathique chez l'homme.* Gaston Doin, Paris, 1927.)

1. Oculomotor nucleus
2. Superior and inferior salivary nuclei
3. Ciliary ganglion
4. Sphenopalatine ganglion
5. Otic ganglion
6. Submaxillary ganglion
7. Oculomotor nerve
8. Trigeminal nerve
9. Facial nerve
10. Glossopharyngeal nerve
11. Auriculotemporal branch of trigeminal nerve
12. Vidian nerve
13. Tympanic branch of glossopharyngeal nerve
14. Chorda tympani nerve
15. Lingual nerve
16. Branch of superficial petrosal nerve containing vasodilator fibers to carotid artery
17. Superior cervical sympathetic ganglion
18. Inferior cervical sympathetic ganglion
19. First thoracic sympathetic ganglion
20. White rami communicantes
21. First and second thoracic nerves
22. Internal carotid artery
23. Vertebral artery
24. External maxillary artery

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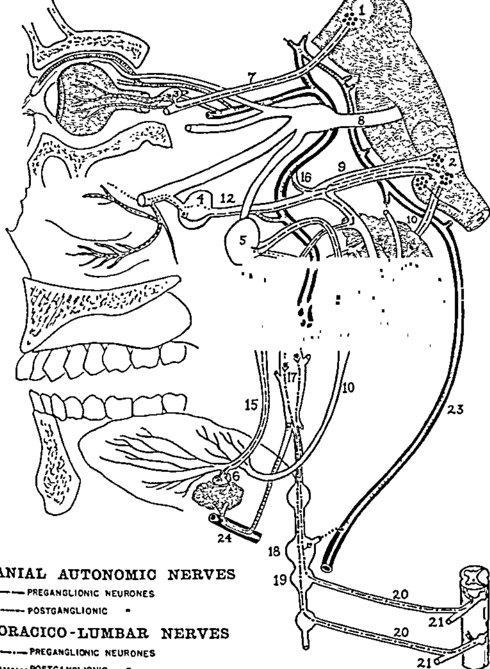


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21. First and second thoracic nerves
22. Internal carotid artery
23. Vertebral artery
24. External maxillary artery

AUTONOMIC INNERVATION OF THE EYE (FIG. 15)

a. Parasympathetic

In the first edition of this book it was stated that preganglionic neurons arise from cells in the Edinger-Westphal nucleus and run in the oculomotor nerve to the ciliary ganglion. G. A. G. Mitchell of Manchester has kindly called our attention to W. E. LeG. Clark's (1926) work on this subject, in which he points out that the cells of this group give rise to no fibers which pass directly to the ciliary ganglion or the eye itself. Therefore, the origin of the preganglionic fibers cannot be located more accurately than in the general area of the oculomotor nucleus.

Postganglionic neurons originate in the ciliary ganglion and run through the short ciliary nerves to the constrictor muscle of the iris and the ciliaris muscle.

Function: Contraction of pupil and accommodation for near vision.

Surgical application: None reported to date.

b. Sympathetic

Preganglionic neurons originate from cells in the intermediolateral column, enter the highest thoracic white rami, and ascend the cervical sympathetic chain to its superior cervical ganglion.

Postganglionic neurons originate from cells in the above ganglion, ascend in the carotid plexus to the ophthalmic division of the fifth nerve, then run via the nasociliary nerve to the eyeball.

Function. Dilatation of pupil and widening of palpebral fissure with some influence on accommodation for distant vision (see p. 250).

Surgical application: Resection of the superior cervical sympathetic ganglion in cases of facial paralysis enables the patient to close his eyelids almost completely.

INNERVATION OF THE LACHRIMAL GLANDS

The pathway of impulses which stimulate the flow of tears has been described by Rowbotham (1939).

a. Parasympathetic

Preganglionic axons: Emerge from the brain stem in the facial nerve (nervus intermedius of Wrisberg) but branch off at the geniculate ganglion. From there they run in the great superficial petrosal and vidian nerves to the sphenopalatine ganglion.

Postganglionic neurons: Cells in Meckel's ganglion send fibers via the zygomaticotemporal branch of the second division of the trigeminal nerve to the lachrimal nerve.

Function: Stimulation of lachrimal cells and vasodilatation.

Surgical application: Abnormal lachrimal function after injury to facial nerve accounts for phenomenon of "crocodile tears" (see p. 250).

b. Sympathetic

Preganglionic neurons are the same as in the case of the eye.

Postganglionic neurons: Axons, which arise from cells in the superior cervical ganglion, ascend along the internal carotid artery. They branch off to the deep petrosal nerve and the vidian. From this point on their course is with parasympathetic fibers.

Function: Vasoconstriction and probably some secretory activity as well. After division of the parasympathetic fibers in the great superficial petrosal nerve, we have observed that only reflex lachrimation is abolished. Some steady secretion still persists.

Surgical application: None.

INNERVATION OF THE SALIVARY GLANDS (FIG. 15)

a. Parasympathetic

Preganglionic neurons to submaxillary and sublingual glands: Cells lie in nucleus salivatorius superior and send their neurons through the facial, chorda tympani, and lingual nerves directly to the submaxillary and lingual glands.

Postganglionic neurons: Cells lie along the chorda tympani nerve.

Preganglionic neurons to parotid gland: The cranial autonomic neurons to the parotid gland arise in the inferior salivary nucleus and leave the brain in the glossopharyngeal nerve. They then pass into the tympanic branch (nerve of Jacobson) to reach the otic ganglion via the lesser superficial petrosal nerve.

Postganglionic neurons: From the otic ganglion the terminal axons reach the parotid over the auriculotemporal branch of the trigeminal nerve.

The anatomy of the salivary pathways has been worked out in dogs. In man Reichert and Poth (1933) have observed that section of either the seventh or ninth cranial nerves causes a decrease in salivary secretion in both the submaxillary and parotid glands.

Function: Increases salivation and dilates blood vessels.

Surgical application: None reported to date.

b. Sympathetic

Preganglionic neurons are the same as in the case of the eye.

Postganglionic neurons: Cells in superior cervical sympathetic ganglion send their fibers along the external carotid and external maxillary arteries to the glands. (See description by Gardner, 1943.)

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Surgical application: None.

INNERVATION OF THE SALIVARY GLANDS (FIG. 15)

a. Parasympathetic

Preganglionic neurons to submaxillary and sublingual glands: Cells lie in nucleus salivatorius superior and send their neurons through the facial, chorda tympani, and lingual nerves directly to the submaxillary and lingual glands.

Postganglionic neurons: Cells lie along the chorda tympani nerve.

Preganglionic neurons to parotid gland: The cranial autonomic neurons to the parotid gland arise in the inferior salivary nucleus and leave the brain in the glossopharyngeal nerve. They then pass into the tympanic branch (nerve of Jacobson) to reach the otic ganglion via the lesser superficial petrosal nerve.

Postganglionic neurons: From the otic ganglion the terminal axons reach the parotid over the auriculotemporal branch of the trigeminal nerve.

The anatomy of the salivary pathways has been worked out in dogs. In man Reichert and Poth (1933) have observed that section of either the seventh or ninth cranial nerves causes a decrease in salivary secretion in both the submaxillary and parotid glands.

Function: Increases salivation and dilates blood vessels.

Surgical application: None reported to date.

b. Sympathetic

Preganglionic neurons are the same as in the case of the eye.

Postganglionic neurons: Cells in superior cervical sympathetic ganglion send their fibers along the external carotid and external maxillary arteries to the glands. (See description by Gardner, 1943.)

Function. Also increases salivation but causes vasoconstriction.

Surgical application: None.

VASOMOTOR SUPPLY OF MENINGEAL AND CEREBRAL ARTERIES

a. Parasympathetic

Vasodilator neurons leave the brain in the facial nerve—Cobb and Finesinger (1932). At the geniculate ganglion these fibers enter the greater superficial petrosal nerve, which, Chorobski and Penfield (1932) have shown, gives off a small group of fibers to the sympathetic plexus on the internal carotid artery.

Sensory neurons: The afferent supply to sensitive structures within the cranium has been mapped by Penfield and McNaughton (1940) above the tentorium. It is derived primarily from the trigeminal nerve with a few fibers from the great superficial petrosal nerve (Gardner *et al.*, 1947). These structures do not belong to the autonomic system. In the posterior fossa the vagus contributes sensory fibers to the region of the jugular bulbs and sigmoid sinuses, and a few others come from the glossopharyngeal nerve

Function: Meningeal and cerebral vasodilatation.

Surgical application: None, in so far as autonomic structures are concerned.

b. Sympathetic (Fig. 15)

Preganglionic neurons: Cells lie in intermediolateral column and send their axons over the upper two thoracic white rami to the stellate and superior cervical sympathetic ganglia.

Postganglionic neurons. These are given off from both ganglia and enter the skull over two pathways.

1. From the stellate ganglion via the vertebral nerve a plexus ascends the vertebral and basilar arteries.
2. A second larger plexus originates from the superior cervical sympathetic ganglion, one division follows the external carotid and middle meningeal arteries to innervate the meninges, and another the internal carotid to the circle of Willis. Gardner (1943), who has made a careful study of the external carotid plexus, states that it is not directly continuous with the filaments along the internal and common carotid arteries, and that periarterial stripping of the latter will not interrupt the sympathetic supply to the face and head. There are two principal branches that leave the superior cervical ganglion, one going directly to the external carotid, the other descending to hook around the superior thyroid artery before it joins the upper branch

Sensory neurons: There is no valid clinical evidence that any afferent fibers from the cervical sympathetic trunk follow the internal carotid

artery, nor that any are supplied to the external branch (see p. 243). Kuntz, however, claims to have anatomical proof for the presence of such fibers in the internal as well as the external and common carotid arteries. This evidence was obtained from tracing degenerating axons in cats after sectioning upper thoracic posterior roots distal to their sensory ganglia.

Function: Meningeal and cerebral vasoconstriction and dilatation (Forbes and Wolff, 1928).

Surgical application: Of possible significance in certain unusual cephalalgias (see Chap. X).

THE CAROTID SINUS PLEXUS (FIG. 16)

The bifurcation of the carotid artery derives a number of afferent fibers from the ganglion nodosum of the vagus and the glossopharyngeal nerves. These terminate in typical sensory end organs in the walls of the carotid bulb (de Castro, 1926, 1928) and carotid body. The main carotid sinus nerve joins the glossopharyngeal, and it has been demonstrated by Code and Dingle (1935) that section of this nerve in the dog removes the regulatory influence of the sinus on the heart rate and blood pressure. This has been found to be equally true in man (Ray and Stewart, 1942). The sinus also receives efferent connections from the superior cervical ganglion of the sympathetic trunk. Hering (1927) and Heymans with his coworkers (1933) have shown that this small plexus has a highly specialized function as a reflex center for controlling blood pressure, heart rate, and respiration (cf. Chap. IV). An excellent description of this plexus with photographs of the structures has been published by Tchibukmacher (1938).

Surgical resection of the sinus has resulted in the cure of recurrent attacks of syncope associated with asystole and rare forms of convulsive seizures.

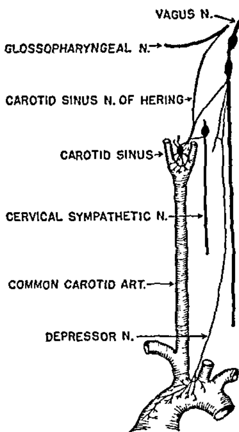


Fig. 16. The carotid sinus nerves. (Redrawn and slightly modified from Heymans, C., Bouckaert, J.-J., and Regniers, P. *Le sinus carotidien et la zone homologue cardio-aortique: Physiologie, pharmacologie, pathologie, clinique*. Gaston Doin, Paris, 1933.)

CARDIAC INNERVATION (FIGS. 14 AND 17)

a. Parasympathetic

Preganglionic motor neurons originate in the dorsal nucleus of the vagus and end in the intrinsic cardiac ganglia.

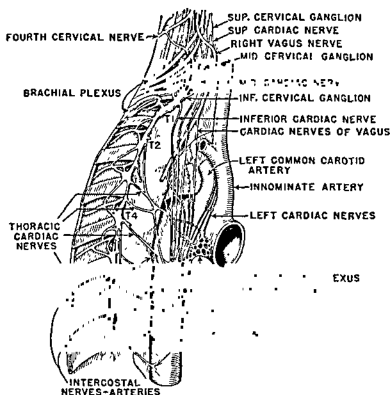


Fig. 17. The nerve supply of the heart. (Modified from Kuntz and Morehouse. Reproduced from P. D White, *Heart Disease*, Macmillan, 1931.) It is doubtful if T5 contributes any significant number of cardiosensory fibers.

Postganglionic fibers run from these ganglia along the coronary arteries.

Afferent axons from the intrinsic cardiac ganglia also reach the ganglion nodosum by the way of the depressor portion of the vagus nerve. In certain animals and occasionally in man, this constitutes a separate trunk, the nerve of Cyon and Ludwig (1866)

Function: Cardiac inhibition and probably constriction of the coronary arteries.

b. Sympathetic

Preganglionic motor neurons come from cells in the intermediolateral column via the anterior spinal roots and upper three to four pairs of white rami communicantes to enter the upper thoracic ganglia. Some of these form synapses at once; others ascend to the cervical ganglia.

Postganglionic neurons leave the ganglionated chain in two divisions: the upper via the superior, middle, and inferior cardiac nerves; the lower by the thoracic cardiac nerves, which have been described by Cannon, Lewis, and Britton (1926), Braeucker (1927), Jonnesco and Enarchesco (1927), Kuntz and Morehouse (1930), and White, Garrey, and Atkins (1933). Both sets of fibers converge in the anterior and posterior cardiac plexuses (Fig. 17).

Sensory neurons, with cells in the upper thoracic posterior root ganglia (especially the second, according to Nonidez, 1939), run via the middle and inferior cardiac nerves, as well as in the thoracic cardiac nerves. These terminate in typical sensory end organs (Stöhr, 1928) in the adventitial plexuses of the aorta and coronary vessels, as well as in the pericardium and the walls of the heart.

Function: Cardiac acceleration and the conduction of cardiac pain. The most widely accepted evidence indicates that these nerves also dilate the coronary arteries.

Surgical application: Relief of pain in coronary thrombosis, angina pectoris, aneurysm of the arch of the aorta, and in the control of paroxysmal tachycardia.

PULMONARY INNERVATION

a. Parasympathetic

The most complete dissections of the nerve supply to the trachea, bronchi, and pulmonary vessels have been carried out by Braeucker (1927).

The preganglionic axons for the most part leave the vagi in the upper mediastinum. In Figure 14 three to four large and many smaller filaments can be seen leaving the vagus and running to the lung hilus. These form synapses with postganglionic neurons in the anterior and posterior pulmonary plexuses which are grouped around the main bronchi.

b. Sympathetic

The preganglionic sympathetic axons follow much the same course as the cardiac supply, except that fewer of them ascend into the cervical sympathetic trunks.

Postganglionic fibers run from the inferior cervical as well as the upper four thoracic ganglia to the pulmonary plexuses.

Function: The action of neither parasympathetic nor sympathetic divisions has been definitely worked out, beyond constriction and dilatation of bronchi (see p. 346).

Surgical application: There are numerous reports of operations on both the vagus and sympathetic trunks for bronchial asthma, but neither method

CARDIAC INNERVATION (FIGS. 14 AND 17)

a. Parasympathetic

Preganglionic motor neurons originate in the dorsal nucleus of the vagus and end in the intrinsic cardiac ganglia.

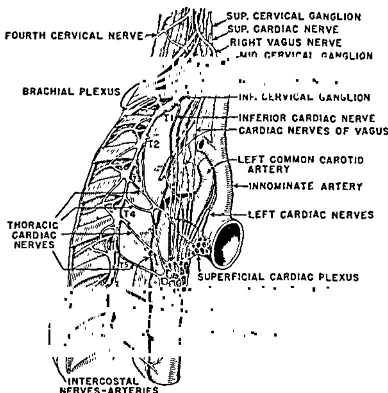


Fig. 17. The nerve supply of the heart. (Modified from Kuntz and Morehouse. Reproduced from P. D White, *Heart Disease*, Macmillan, 1931.) It is doubtful if T5 contributes any significant number of cardiosensory fibers.

Postganglionic fibers run from these ganglia along the coronary arteries.

Afferent axons from the intrinsic cardiac ganglia also reach the ganglion nodosum by the way of the depressor portion of the vagus nerve. In certain animals and occasionally in man, this constitutes a separate trunk, the nerve of Cyon and Ludwig (1866).

Function: Cardiac inhibition and probably constriction of the coronary arteries.

b. Sympathetic

Preganglionic motor neurons come from cells in the intermediolateral column via the anterior spinal roots and upper three to four pairs of white rami communicantes to enter the upper thoracic ganglia. Some of these form synapses at once; others ascend to the cervical ganglia.

the semilunar (celiac), aorticorenal, and superior mesenteric ganglia are described as separate structures in every textbook of anatomy (Fig. 18), it must be remembered that this is only a schematic representation and that the ganglia may actually be fused or split up into every conceivable variation.

a. Parasympathetic.

Preganglionic neuron cells lie in the dorsal vagal nucleus and send axons along the vagi to end in the intrinsic visceral plexuses. These are designated as the phrenic, adrenal, spermatic or ovarian, gastric, hepatic, and superior mesenteric plexuses (Fig. 18). In the case of the intestine, it is probable



Fig. 18. The abdominal nervous plexuses. (Modified from Hovelacque, A. *Anatomie des nerfs craniens et rachidiens et du système grand sympathique chez l'homme.* Gaston Doin, Paris, 1927.)

has proved strikingly successful to date. Painful cough reflexes in bronchial carcinoma can be eliminated by vagectomy (see p. 349).

ESOPHAGEAL INNERVATION

a. Parasympathetic (Fig. 14)

The thoracic esophagus receives its cranial autonomic innervation over a large number of small filaments directly from the vagus nerves. The best descriptions of the distribution of the vagi to the esophagus and stomach have been written by G. A. G. Mitchell (1938*A*), Professor of Anatomy at Manchester, and by surgeons interested in vagotomy for control of peptic ulceration—Dragstedt, Fournier, *et al.* (1947), Walters and associates from the Mayo Clinic (1947), Chamberlin and Winship (1947), and Doubilet *et al.* (1948).

Function: Stimulation of peristalsis and conduction of sensation from the upper thoracic and cervical portions.

b. Sympathetic

Sympathetic motor as well as viscerosensory fibers leave the cord mainly from its fifth and sixth thoracic segments. According to Knight (1934), dissections of stillborn infants show that the upper portion of the thoracic esophagus derives a few direct branches from the sympathetic ganglia at the level of the aortic arch. Immediately above the diaphragm no direct fibers run to the esophagus. This lower portion, as well as the cardiac sphincter, derives its innervation via the periaortic plexus and the splanchnic rami which run through the celiac ganglia and along the branches of the celiac axis (principally the left gastric artery).

Function. Motor activity is slight, but pain may be transmitted from lower portion of esophagus over sympathetic and splanchnic nerves.

Surgical application: None.

INNERVATION OF THE UPPER ABDOMINAL VISCERA

(See also the anatomical description of the splanchnic innervation on p. 34.)

Valuable descriptions of the nerve supply of the biliary system are available by W. F. Alexander (1940) and Womack and Crider (1947) and of the stomach by McCrea (1926) and Mitchell (1938*A*). The celiac or solar plexus is the central distributing center for both the splanchnic nerves and the vagi. In addition, it receives connections from the uppermost lumbar ganglia—perhaps from the phrenic nerve as well (Hovelacque, 1927). The plexus is made up of a dense meshwork of fibers around the aorta at the origin of the celiac axis, renal, and superior mesenteric arteries. While

Surgical application: Section of the lower vagi reduces the tendency to gastric and duodenal ulceration by diminishing the cephalic phase of secretion and motility.

b. Sympathetic

Preganglionic cells lie in the intermediolateral column (Fig. 19). Their axons traverse the lower five to seven pairs of thoracic white rami (Fig. 12), pass through the sympathetic trunk ganglia, for the most part without interruption, and along the splanchnic nerves to end in the preaortic ganglia. The celiac ganglia usually consist of two large semilunar masses on either side of the celiac axis with connections to lesser subsidiary ganglia grouped around the arteries to the other upper abdominal organs (Figs. 18 and 19).

Postganglionic fibers leave the celiac and other related ganglia to run with the vagal fibers along the periarterial visceral plexuses. In the peculiar case of the adrenal glands the preganglionic axons are not interrupted in extrinsic ganglia, but end around the chromaffin cells of the adrenal medulla. Presumably, these postganglionic cells have taken on a secretory function. In addition to the minor splanchnic nerves from the tenth and eleventh thoracic segments, further filaments to the adrenal glands are given off from the twelfth thoracic and first (and possibly second) lumbar segments (Maycock and Heslop, 1939).

Afferent pathways, with their cells in the lower six pairs of thoracic posterior root ganglia, follow a corresponding course along the sympathetic pathways to sensory endings in the mesenteries and walls of the hollow viscera (Fig. 19). Some of these fibers end in the Pacinian corpuscles (Sheehan, 1932), others in fine beaded terminals.

Function: Inhibition of peristalsis, secretion, and vasoconstriction. The afferent fibers carry subconscious reflex stimuli, the feeling of nausea, and the pain of distention from the hollow viscera.

Surgical application: Relief of pain from the upper abdominal viscera in conditions not amenable to direct surgical attack.

INNERVATION OF THE PELVIC VISCERA

a. Parasympathetic

Preganglionic neuron cells lie in the lateral portion of the anterior horn of the sacral cord. Thence their axons run out over the second, third, and fourth sacral anterior roots and the sacral nerves, to emerge from the sacral foramina in the hollow of the sacrum. Their rami, the nervi erigentes, pass through the inferior hypogastric ganglia. The distribution of these fibers was formerly supposed to be limited to the pelvic viscera. Mitchell

that the fibers terminate around the ganglion cells of Auerbach's mesenteric and Meissner's submucous plexuses (Fig. 19).

Function: To stimulate peristalsis, secretion, and vasodilatation of the digestive glands While the vagi carry some afferent reflex stimuli and a part of the sensation of nausea, they are not known to carry any definite pain sensation.

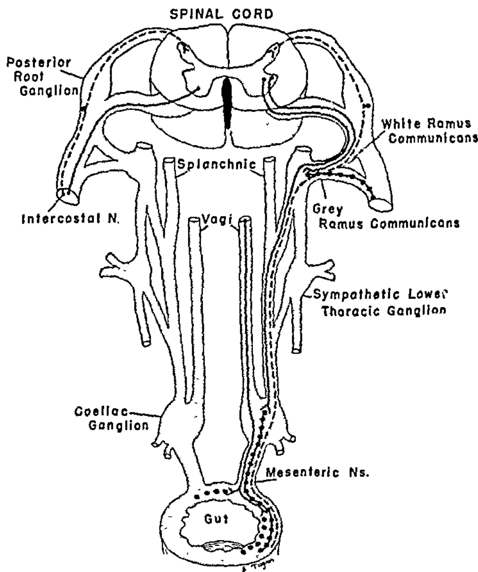


Fig. 19. Diagram of vagal and splanchnic innervation of upper gastrointestinal tract.

Left side. Somatic
——— Skeletal motor neuron
- - - - Somatic sensory neuron

Right side. Visceral
——— Autonomic preganglionic motor neuron
— — — Sympathetic postganglionic motor neuron
. .... Parasympathetic postganglionic motor neuron

pass, may benefit the neurogenic form of megacolon. Excision of the superior hypogastric plexus relieves the pain of essential dysmenorrhea but is ineffective in painful conditions of the bladder (see p. 389).

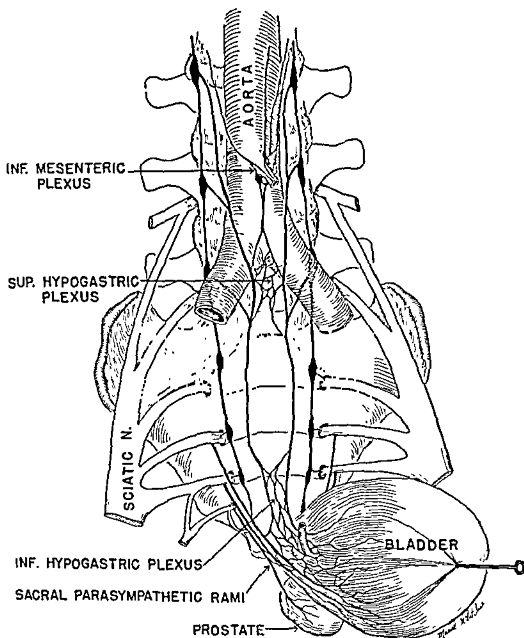


Fig. 20. The inferior mesenteric and hypogastric plexuses.

INNERVATION OF THE PERIPHERAL ARTERIES, SWEAT GLANDS, AND ERECTOR PILI MUSCLES

a. Parasympathetic

Investigations by Hinsey (1934), Westbrook and Tower (1940), and others (see p. 80) indicate that the vasodilator action of the posterior

(1935*A*), however, has traced a number of ascending strands which carry parasympathetic axons via the inferior mesenteric plexus to the descending colon Parasympathetic innervation of the uterus, tubes, ovaries, and testes has been demonstrated by Reynolds (1939), Mitchell (1938*B*), Goecke (1938), and Wein (1939).

Postganglionic neurons constitute the intrinsic plexuses in the muscular walls and internal sphincters of the bladder and rectum, as well as in the genital organs

Function. Contraction of the bladder and lower colon with control of the vesical and anal sphincters. Vasodilatation. There are also myelinated sensory axons in these nerves which carry pain from the bladder, prostate, and cervix uteri.

Surgical application: Section of the lower sacral posterior roots, chemical destruction of their fibers by intrathecal injection of alcohol, or resection of the inferior hypogastric plexus may be used as a last resort in painful malignant conditions of the pelvic viscera, but these operations paralyze the voluntary power of micturition and control of the anal sphincter.

b. Sympathetic

Preganglionic cells lie in the lowest thoracic and upper lumbar levels of the intermediolateral column. These cells send their axons out over the lower white rami of the thoracolumbar outflow to the lumbar and preaortic ganglia.

Postganglionic neurons originate in the sympathetic trunks, as well as in the preaortic ganglia, to form a plexus descending along the abdominal aorta (Fig. 20). At the level of the inferior mesenteric artery there are two small ganglia, and from them a plexus descends this artery to innervate the sigmoid and rectum. The remainder of the descending sympathetic fibers form the superior hypogastric plexus at the bifurcation of the aorta. This divides into the two hypogastric nerves which run in the hollow of the sacrum to join the inferior hypogastric plexus. An excellent surgical description of the superior hypogastric plexus has been given by Dobrzaniecki and Serafin (1934).

Sensory fibers from the posterior root ganglia in the same segments of the cord run directly into the superior and inferior hypogastric plexuses.

Function: Vasoconstriction and contraction of smooth muscle in the bladder neck, prostate, seminal vesicles and rectum. Ejaculation of semen Inhibition of peristalsis in the lower colon. Transmission of uterine pain.

Surgical application: Resection of the lumbar ganglia which give rise to these fibers, or the ganglia at the root of the inferior mesenteric artery and the superior hypogastric plexus through which the sympathetic impulses

ment. The first is recent, more exact information concerning the segmental level of vasomotor and sudomotor outflow. Past teaching has localized this to the anterior thoracic roots from T2 to T8. By stimulating the ventral rootlets at operation and measuring changes in cutaneous resistance,

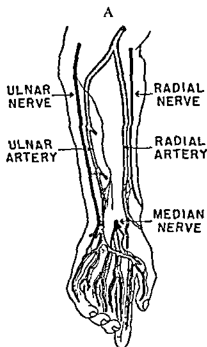
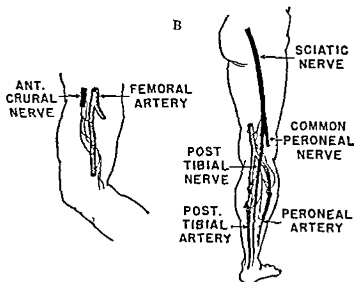


Fig. 21.

A. The nerve supply of the arteries of the forearm and hand. *(Redrawn from Kramer* and Todd, 1914, courtesy of *Anatomical Record.)*

B. The nerve supply of the arteries of the leg (Modified from Potts, L. W. "The distribution of nerves to the arteries of the leg." *Anat. Anz., 1914, 47: 138–144, courtesy of* Gustav Fischer, Jena.)



Ray, Hinsey, and Geohegan (1943) found that sympathetic efferent impulses may emerge as low as T10. The upper limit is nearly invariably over the second thoracic root. In only 1 out of 11 individuals, and in that case only from the left side, a response was obtained on stimulation of T1. On the basis of experiments made on cats, dogs, and monkeys Kuntz (1949)

spinal roots does not depend on the presence of a parasympathetic outflow from the spinal cord, as suggested by Kuré (1931). The phenomenon of dermatomal flushing, observed by Bayliss (1901) on stimulation of posterior spinal roots, must still be regarded as an example of antidromic conduction along sensory axons. With the exception of the blood vessels in the penis and possibly other erectile tissues, there is no parasympathetic supply to the peripheral blood vessels. Flushing of the face from embarrassment may be an exception to this statement, as it is not affected by cervical sympathectomy. There are also no parasympathetic fibers to the erector pili muscles, and no known connections with the sweat glands except in the skin around the mouth (List and Peet, 1939).

b. Sympathetic

Preganglionic neurons arise from the entire thoracolumbar portion of the intermediolateral column. Their axons emerge over the anterior roots and white communicant rami to terminate in all the ganglia of the paravertebral sympathetic chains

Postganglionic neurons leave these ganglia in two ways:

1. Directly to the larger arteries of the trunk to form periarterial plexuses, e.g., along the aorta, carotid, subclavian (annulus of Vieussens), and iliac vessels. These plexuses do not descend far beyond the axilla and Poupart's ligament, but they do ascend along the carotid and vertebral arteries to the head.
2. Gray rami run back into the cervical, the intercostal, and the lower spinal nerves, and their axons are distributed in a segmental manner to the sweat glands, hair follicles, and all the arteries of the trunk and extremities (Figs. 21 A and 21 B). Krogh (1929) has shown that the terminal ramifications of these unmyelinated axons run to the individual capillaries.

Sensory innervation of the arteries: R M Moore and Singleton's (1933) experiments have shown that painful stimuli from the visceral arteries are transmitted over sensory axons in the splanchnic and other sympathetic nerves, but that pain from the peripheral arteries traverses the spinal sensory nerves This has been confirmed in conscious human patients in whom the lumbar chain has been stimulated in the course of operations under local anesthesia and postoperatively by means of pull-out electrodes In these observations in which the patients felt clear-cut abdominal pain (White, Sweet, and Simeone), we have never been able to elicit any radiation to the lower extremities.

Surgical applications. Resection to increase blood flow in the extremities and for the relief of excessive sweating

In connection with the sympathetic supply to the upper extremity, several points of anatomical importance to the surgeon deserve special com-

on the sympathetic nerves. For further details, there are a number of excellent books available, among which the following have been frequently quoted and deserve special mention: Hovelacque's textbook of neuroanatomy (1927) for a complete discussion of gross anatomy and its excellent plates by Moreau; Ranson's *Anatomy of the Nervous System* (1947) for an account of the finer neurohistological arrangement; and Kuntz's *Autonomic Nervous System* (1945) and his more recent (1949) condensed outline of sympathetic neuroanatomy for a general anatomical, physiological, and pathological consideration of the involuntary nerves.

and his coworkers claim that a significant number of fibers traverse the first thoracic root and that these are responsible for persistent vasoconstriction after operations where the first thoracic ganglion has been left intact. In particular, they stress the point that these residual pathways are of importance after interruption of all other preganglionic fibers below the first thoracic level Experiments made on animals do not necessarily apply to man, yet if delicate methods of testing are used, it is still possible that a relatively few sympathetic impulses may be traced to the first thoracic root. The observations of Netsky (1948) with his prism method of testing activity in individual sweat glands points in this direction. If the relatively few remaining fibers can increase their activity with time, and if these fibers supply arteriolar smooth muscle as well as sweat glands, their presence may account in part for the persistence of vasoconstrictor activity in the "sympathectomized" upper extremity (see p. 196).

Another possible cause of failure is the existence of sympathetic pathways outside the paravertebral ganglionic trunks. The existence of such by-passes via intermediate ganglia has been reported by Wrete (1934), Skoog (1947), and Kuntz (1949) after careful microscopic examination of the lumbar and cervicothoracic spinal outflow in human cadavers (see text on p 31 and Fig. 11, above). This undoubtedly accounts for the persistence of anterior thigh sweating in small amounts after complete thoracolumbar sympathectomy, which we have often observed and which Ray and Console (1948) have shown is abolished by cutting or blocking the anterior lumbar roots or the lumbar nerves, or by interrupting residual ganglionic synapses with tetraethylammonium chloride.

In early attempts to sympathectomize the upper extremity, the operation was frequently limited to stellectomy. This left intact important rami connecting the second and sometimes the third thoracic ganglia with the lower portion of the brachial plexus. Telford and Stopford (1931) have ascribed the vascular disturbances so often encountered in individuals with cervical ribs to irritation of vasoconstrictor fibers concentrated in the lower part of the plexus by the underlying rib. Recently, Sunderland (1948) has studied this question and found such a wide dispersal of the sympathetic fibers throughout the lower cord of the plexus that this complication cannot be caused by mechanical irritation from pressure on exposed vasoconstrictor fibers at the site where the plexus is related to the abnormal rib.

This anatomical outline has been set down as briefly as possible because this ground will be covered again, both in the following chapter on physiology and from another point of view in the discussion of surgical procedures

hair; at the same time it increases the production of heat by raising the blood sugar and the oxidative processes of the body.

When a warm-blooded animal is faced with a deficiency of oxygen, either through severe exertion or because of an ascent to high altitudes, or through the action of a gas like carbon monoxide, the sympathicoadrenal system comes to the rescue. The heart is made to pump more rapidly, the great splanchnic area where blood accumulates during digestion is emptied by vasoconstriction, and the blood is shunted to essential structures. Finally, by contraction of the spleen, millions of stored red blood cells are mobilized to help carry a greater oxygen supply. J. Barcroft, Nisimaru, and Puri (1932) have shown that this is brought about in part by the major splanchnic nerves and also by the increase of adrenine in the circulating blood.

After prolonged periods of strenuous muscular exertion, the body sugar may be greatly reduced and the liver dangerously depleted of its glycogen reserve. Should the blood sugar fall below 45 mg per cent, as a result of either prolonged fatigue or excess of insulin, convulsions leading to coma and death might follow. Before such a dangerous state is reached the sympathicoadrenal system comes to the rescue by withdrawing further stores of glycogen from the liver and, unless the reduction is overwhelming, the blood sugar is maintained at a safe level. These same autonomic mechanisms free the laboring muscles of an excess of lactic acid and thereby protect the body from acidosis. Another by-product, heat, which is produced in enormous quantities by muscular work, is eliminated by stimulation of the sweat glands and by dilatation of the peripheral vascular bed.

When considerable portions of the ganglionated chains and splanchnic trunks are resected by the surgeon, sympathetic activity in remaining areas is increased. Thus, after denervation of the extremities, there is often troublesome sweating in the remaining areas of skin with intact nerve supply; and after more extensive thoracolumbar ganglionectomy and splanchnicectomy, vasoconstrictor tone in the upper extremities is greatly increased. In this way the higher regulatory centers in the hypothalamus attempt to compensate for impairment of heat elimination and control of blood pressure

Of particular interest to the surgeon is the response of the sympathicoadrenal system to combat the damages resulting from severe accidents or operations Here a number of protective reactions come to the rescue. In case of hemorrhage, generalized peripheral vasoconstriction maintains blood flow through the vital organs. The tendency to asphyxia, acidosis, dehydration, and loss of body heat which follow general anesthesia and

CHAPTER IV

General Physiology

In the preceding chapter it has been pointed out that the autonomic nervous system innervates nonstriated muscle and glands which are not under the voluntary control of the cerebral cortex. These comprise the iris, the lachrymal, sudatory, and digestive glands, and the heart and blood vessels, as well as tubular viscera such as the bronchi and the gastrointestinal and genitourinary tracts. It should be remembered that each of these structures, as a rule, receives a dual innervation, in part from the cranial or sacral division of the parasympathetic system, in part from the thoracolumbar outflow of the sympathetic. The purpose of this chapter is to outline the function of these two systems in the living organism. This will be taken up from the viewpoint of the physiologist rather than from that of the surgeon. The practical application of this knowledge and the details that are of special use in the clinic have been reserved for later chapters.

I. Homeostasis

The first approach to this subject was made by Claude Bernard (1878) who pointed out that, unlike the cold-blooded animals, mammals are independent of the medium which surrounds them. The greater adaptability of the warm-blooded animals to life in different surroundings is due in great part to the more efficient regulation of their vegetative processes by the involuntary nervous system. Man, in common with other mammals, is separated from his surroundings by a thin layer of dead cells or a film of mucus and salt solution. Within these walls he maintains his fluid matrix in a remarkably constant state. It was the great French physiologist who saw that the constant preservation of this "*milieu intérieur*" was the determining factor of our free and independent life. This personal, individual climate, which we carry about with us, must not change if we are to continue in a state of health. For example, external cold, which forces insects and reptiles to hibernate, stimulates the sympathicoadrenal system of birds and most mammals to resistance. It prevents loss of heat by radiation through constriction of the peripheral arteries and by erection of the feathers or

hair; at the same time it increases the production of heat by raising the blood sugar and the oxidative processes of the body.

When a warm-blooded animal is faced with a deficiency of oxygen, either through severe exertion or because of an ascent to high altitudes, or through the action of a gas like carbon monoxide, the sympathicoadrenal system comes to the rescue. The heart is made to pump more rapidly, the great splanchnic area where blood accumulates during digestion is emptied by vasoconstriction, and the blood is shunted to essential structures. Finally, by contraction of the spleen, millions of stored red blood cells are mobilized to help carry a greater oxygen supply. J. Barcroft, Nisimaru, and Puri (1932) have shown that this is brought about in part by the major splanchnic nerves and also by the increase of adrenine in the circulating blood.

After prolonged periods of strenuous muscular exertion, the body sugar may be greatly reduced and the liver dangerously depleted of its glycogen reserve. Should the blood sugar fall below 45 mg per cent, as a result of either prolonged fatigue or excess of insulin, convulsions leading to coma and death might follow. Before such a dangerous state is reached the sympathicoadrenal system comes to the rescue by withdrawing further stores of glycogen from the liver and, unless the reduction is overwhelming, the blood sugar is maintained at a safe level. These same autonomic mechanisms free the laboring muscles of an excess of lactic acid and thereby protect the body from acidosis. Another by-product, heat, which is produced in enormous quantities by muscular work, is eliminated by stimulation of the sweat glands and by dilatation of the peripheral vascular bed.

When considerable portions of the ganglionated chains and splanchnic trunks are resected by the surgeon, sympathetic activity in remaining areas is increased. Thus, after denervation of the extremities, there is often troublesome sweating in the remaining areas of skin with intact nerve supply; and after more extensive thoracolumbar ganglionectomy and splanchnicectomy, vasoconstrictor tone in the upper extremities is greatly increased. In this way the higher regulatory centers in the hypothalamus attempt to compensate for impairment of heat elimination and control of blood pressure.

Of particular interest to the surgeon is the response of the sympathicoadrenal system to combat the damages resulting from severe accidents or operations. Here a number of protective reactions come to the rescue. In case of hemorrhage, generalized peripheral vasoconstriction maintains blood flow through the vital organs. The tendency to asphyxia, acidosis, dehydration, and loss of body heat which follow general anesthesia and

prolonged operations are all combated by the thoracolumbar division of the autonomic nervous system.

In connection with the activity of the sympathetic nervous system in conditions which bring about the clinical picture of shock, an observation of unusual interest has been reported by N. E. Freeman (1933). He showed in animal experiments that prolonged activity of the sympathetic nervous system results in a decrease in volume of the circulating blood. If true, such a concept would be of fundamental importance because it would signify that, if an emergency is too severe or too long continued, the very factors which normally act to preserve the organism may lead to its dissolution. Schafer (1944), however, has been unable to confirm this observation. In recent experiments on dogs in which intense and prolonged vasoconstriction had been produced by resection of the aortic-depressor nerves and carotid sinuses, they tolerated hemorrhage approximately as well as normal controls. Schafer stated that the experience at the University of Chicago failed to support the theory that sympathicoadrenal activity per se can lead to shock.

A great part of the work which has led to our present understanding of the physiology of the sympathetic nervous system has been carried out by Cannon during his thirty years as professor of physiology at Harvard Medical School. Working first on the reaction of the body to fear, rage, etc. (1929*A* and 1932), he came gradually to the appreciation of the wider importance of this system in adapting every adjustment of the body to the difficult situations which constantly confront us. One of his greatest contributions to this subject was his observations on animals which had been totally deprived of sympathetic activity by removing the paravertebral ganglia from the neck to the lower lumbar regions (Cannon *et al.*, 1929). These animals (cats) lived in the sheltered conditions of the laboratory in good health for years The animals became very sensitive to cold, as they lost the ability to conserve heat. Erection of the hairs was permanently lost, but the peripheral arteries recovered a degree of local vasomotor tone. Ability to perform muscular work and to resist fatigue was greatly reduced. These animals showed no tendency toward vagotonia, as digestion was unchanged, the heart rate was only slightly slowed, and the blood pressure remained little altered. The basal metabolic rate was reduced about 10 per cent. The cats became pregnant and reproduced in a normal manner, but they were unable to nurse their young (Cannon and Bright, 1931). There were no noticeable growth changes in kittens which had a total sympathectomy performed on one side. This shows that the sympathetic nervous system is relatively unimportant in a protected con-

stant environment, but emphasizes its essential character in the conditions of stress which are met in normal existence.

In summing up the role of the thoracolumbar division, we should think of it as an emergency protective mechanism, which may not be functioning all the time, but which is always ready to go into action to combat any variety of adverse circumstance. Some of the most common conditions which arouse its activity are pain, extremes of temperature, asphyxia, hemorrhage, infection, dehydration, and hypoglycemia. Furthermore, any form of intense emotion or psychic trauma may stimulate a generalized sympathicoadrenal discharge. Cannon (1933) emphasized the interesting fact that this mechanism may actually be harmful unless the emotion is transformed into action. "If no action succeeds the excitement and the emotional stress—even worry or anxiety—persists, then the bodily changes due to the stress are not a preparatory safeguard . . . but may be in themselves profoundly upsetting to the organism as a whole." Little attention has been paid to this effect by the medical profession, although it is of profound importance in human psychology. An understanding of the manner in which our involuntary nervous system reacts demands that we either permit our excitement to find appropriate expression without repression or learn to take an objective attitude which will counteract its deleterious effects. If the emotion cannot be controlled, Cannon suggested that the best thing to do is to work off the bodily changes which have occurred by hard physical exercise. In this way, if it is a matter of a temporary emotional upset, the body may be restored to normal. This same point has been aptly expressed by Fulton (1936*A*) in the statement that "the heart and circulation may be worked just as hard, and just as much as a detriment to the body as a whole, from an arm chair . . . as from a rower's seat." The deleterious effects which can be produced when the cortex loses its control over the more primitive autonomic centers in persons who are victims of nervous exhaustion or degenerative disease have been emphasized by Alvarez (1940).

Since the functions of the sympathetic nerves are catabolic and give rise to an extraordinary liberation of body energy, they are of a spendthrift character. Of equal importance to the body are the anabolic functions of the craniosacral (parasympathetic) division which come into play during the periods of rest and recuperation and are of a conservative character. In summing up their activity we shall again make extensive use of Cannon's excellent exposition in *The Wisdom of the Body* (1932). The functions of the cranial divisions are carried out by a group of reflexes, conservative, protective, and up-building in their service. By narrowing the pupil, the

retina is protected from excessive light. By providing for the flow of saliva and gastric juice, and by increasing the tonic state of the gastrointestinal canal, proper digestion, absorption, and elimination of food substances are assured. Further evidence of the conservative influence of cranial autonomic tone is seen in the provision for rest and recuperation of the cardiac muscle by vagal slowing of the heart rate.

The function of the sacral division is in the main to empty hollow organs which are periodically filled. Sacral autonomic impulses cause contraction of the lower colon, rectum, and urinary bladder, simultaneously relaxing the anal and vesical sphincters. Penile erection is mediated by the nervi erigentes, while ejaculation and subsequent vasoconstriction of the corpora cavernosa are brought about by opposing sympathetic impulses.

The experimental work of W. R. Hess (1948) in Zurich, which has won him the Nobel prize, confirms Cannon's earlier concepts of a balanced control by the two divisions of the autonomic system. In addition to their regulation of catabolic activity in times of stress and anabolic role in the periods of rest and repair, Hess has emphasized that both may exert their characteristic influences in the psychic field, as well as on the soma.

It is apparent that these two great systems, which control the activity of our circulatory, respiratory, digestive, and genitourinary systems, are in a state of balanced opposition. Like the balanced tone of the extensor and flexor groups of muscles described by Sherrington, when one is excited, the other is inhibited. While the effect of the sympathetic impulses is very diffuse, the opposed effect of the parasympathetic is more specific.* Between the two, every type of response, both general and local, is provided for. As Cannon put it,† "all the viscera can be influenced simultaneously in one direction or the other by varying, up or down, the . . . tonic activity of the sympathetic division. And any special viscus can be separately influenced . . . by varying . . . the tonic activity of the special nerve of the opposed cranial or sacral division that reaches directly to the viscus. Thus the heart may beat rapidly because the effect is part of the total complex of effects on the viscera produced by the sympathetic in emotional excitement; . . . or it may beat rapidly without extensive involvement of other viscera because of a lessening of vagal inhibition. The sympathetic is like the loud and soft pedals, modulating all the notes together; the cranial and sacral innervations are like the separate keys. When we con-

* See Chap III. It has been shown that the preganglionic sympathetic neurons end in the paravertebral or celiac ganglia, where they form synapses with a large number of postganglionic neurons, which are widely distributed In contrast to this the parasympathetic neurons reach the viscera directly and synapse in the terminal plexuses with much shorter and more circumscribed postganglionic fibers.

† Cannon, W B *The wisdom of the body.* W. W. Norton, New York, 1932.

sider that in emergencies the sympathetic functions in a great variety of ways to serve the organism as a whole, the importance of its arrangement for simultaneous and unified action becomes evident."

This co-ordinated activity of the body as a whole to meet changing conditions in its external or internal environment by autonomic adjustments has been called "homeostasis" by Cannon (1929*B*). To the modern generation of medical students brought up on the concept that the parasympathetic and sympathetic divisions of the autonomic nervous system are of exactly equal importance in the nicely balanced control of homeostasis, Langworthy's (1943) critique of the general principles of autonomic innervation will be most provocative reading. He points out that in such dually innervated organs as the iris and the urinary bladder, the parasympathetic is of paramount importance in the innervation of smooth muscle, while the sympathetic exerts its influence solely through the medium of the circulation. The bladder is certainly an exception to Cannon's postulate of dual innervation, as its filling and emptying are controlled solely through the activity of the sacral parasympathetic outflow. In the case of the iris, however, Langworthy's concept that pupillary dilatation is mediated through inhibition of its parasympathetically innervated circular muscle and that the only action of the sympathetic is to constrict the blood vessels of its spongy vascular tissue is not a satisfactory explanation. White (1948) has summarized conclusive evidence for the existence of radially arranged pupillary-dilator muscle fibers under direct sympathetic control. Langworthy's conclusion that there is no real antagonism between the two systems appears to be true only in the case of the bladder. He has not produced convincing proof against the dual control of the iris, nor any evidence whatever against the balanced control of other important organs such as the heart, which has been established quantitatively by Rosenblueth and Simeone (1934). We believe it is probable that the theory of homeostasis, built up on such careful experimental evidence by Claude Bernard, Cannon, and many other noted physiologists, is destined to stand the test of time.

With advancing age and certain abnormal states, the control of homeostasis becomes less efficient. Lasch and Müller-Deham (1930) found that maintained vagal tone and diminished sympathetic activity cause a vagus preponderance in old age. All automatic mechanisms, even the most efficient, may cease to function smoothly. The normally efficient homeostatic control may break down in certain abnormal conditions. For example, many individuals suffer from chronic vasoconstriction in the extremities; their hands and feet are constantly cold and moist from exces-

sive perspiration. In other instances the heart may overaccelerate at the slightest stimulus, or food may fail to progress along the gastrointestinal canal at a normal rate. When these extreme reactions continue, they result in clinical syndromes such as acrocyanosis and nervous sweating of the palms and soles, neurocirculatory asthenia, cardiospasm, and gastroduodenal ulceration, as well as in a host of vague symptoms which cannot be classified under any definite diagnosis. Surgeons with a keen insight into the physiology of the autonomic nervous system have been able to devise methods of controlling a number of these abnormal states by paralyzing the nerves which bring them about.

A final point of academic interest concerns the rare instances of voluntary control of visceral function. Favill and White (1917) found reports of 13 persons with some voluntary control of cardiac acceleration. The patient studied by them could accelerate his heart from 98 to 161 beats per minute. This was a direct sympathetic pressor effect and was not brought about by vagal inhibition, as he could still accelerate 20 beats after atropinization. Blood pressure rose simultaneously from 124/80 to 146/110, and there was concomitant pupillary dilatation. Examples of other individuals who could initiate and stop attacks of paroxysmal tachycardia and dilate their pupils chiefly through voluntary sympathetic control are recorded in this article. Ability to produce piloerection in addition to cardiovascular and pupillary pressor responses has been reported by Lindsley and Sassaman (1938).

II. Methods by Which the Autonomic Nervous System Regulates Homeostasis

As in the somatic system, autonomic reflexes are integrated by the central nervous system at different anatomical levels. This interesting analogy was developed by Fulton (1939), who pointed out that only simple vasomotor, visceral, and sexual reactions are integrated at the spinal level, whereas in the medullary stratum are organized the reflexes concerned with the maintenance of a constant blood pressure. Other combined reactions such as salivation and vomiting, also developed at this level, represent combined reactions of the autonomic and somatic systems. The hypothalamic level is far more complex. Here take place temperature regulation, determination of estrus, and control of carbohydrate, fat, and water metabolism. Fulton further summarized the evidence for a rich and varied representation of autonomic activities in the cerebral cortex. Disturbances of visceral activity which have been produced by lesions of the frontal

areas indicate that in man the hypothalamic level is under the direct control of the cortex.

According to Cobb (1949), who has recently reviewed the psychology of emotional responses and the physiological responses set up in the viscera, glands, and muscles, "the hippocampus is not an olfactory organ, but a special sort of cortex that integrates visceral and other somatic afferents with smell and taste. There is evidence that this area discharges into the hypothalamus, thence to thalamus, cingulum, and neocortex, and gives a background for emotional feeling and expression. Closely related are the sympathetic discharges of the hypothalamus to midbrain, hindbrain, and spinal cord. And most important is the hypothalamic control over the pituitary."

Autonomic Representation in the Cerebral Cortex. In the normal experiences of everyday existence, disagreeable smells, tastes, sights, sounds, and emotions are a frequent cause of disturbances in the autonomic mechanisms. These upsets include such common effects as loss of appetite after tasting a bad egg or fainting at the sight of blood. These manifestations are due to cortical reflexes mediated through connections with the lower autonomic centers in the hypothalamus.

Over seventy years ago, Hughlings Jackson (1876) suspected that visceral functions must have extensive representation in the cerebral cortex, since these functions are almost invariably disturbed during epileptic seizures. While a number of investigators—Eulenburg and Landois (1876), Bechterew and Misslawsky (1886), Ellis and Weiss (1936)—have observed a primary rise in cutaneous temperature of the opposite side of the body following ablation or vascular injuries of the precentral area in the frontal lobe, thermocouple determinations of intramuscular temperatures recently reported by Pennes (1949) show no consistent temperature changes in the resting limbs in cases of chronic unilateral cerebral hemiplegia. There is, however, a prompt elevation in temperature when sustained activity is induced in spastic muscles, such as occurs during ankle clonus. Kennard (1934) has reported a fall in temperature in monkeys following unilateral excision of the precentral cortex. Fulton (1936*B*) attributes this cooling response on ablation of area 6 to the paralysis of the mechanism of reflex vasodilatation in the activated muscles, which he believes is a normal response in connection with motor activity mediated by area 4. In man, Bucy (1935) has corroborated Kennard's findings on the basis of a number of clinical reports and observations of an instructive case. He concludes that vasoconstriction is often produced

in cerebral hemiplegia through interruption of inhibitory impulses from the cortex to the vasoconstrictor centers of the hypothalamus and medulla.

Experimental stimulation of the cerebral hemispheres by Hoff and Green (1936) and Green and Hoff (1937) has disclosed a definite cortical influence on the lower autonomic centers. These investigators concluded that * "there is a mechanism by which the cortex (motor and premotor) can influence the state of the cardiovascular system, and that through this mechanism the cortex may bring about a finer adjustment of the activity of the heart and circulation in accordance with the exigencies of the external environment and the immediate activities of the skeletal musculature." In addition to cardiovascular effects, stimulation of the premotor area and certain adjacent parts of the cerebral cortex in monkeys has produced an increase of intestinal peristalsis, whereas bilateral extirpation has caused stasis and, in several instances, has been followed by intussusception (Watts and Fulton, 1934). Apparently, there are no separate cortical areas for sympathetic and parasympathetic reactions, but the character of the reaction is dependent upon the general physiological state of the organism (Crouch and Thompson, 1939). In summing up present theories, Fulton (1936*B*) states that "the coexistence in the same anatomical area of the cortex of autonomic and of somatic representation makes possible simultaneous and appropriate adjustments such, for example, as are necessary for heat regulation. . . . Undoubtedly this overlapping also facilitates other cortically integrated reactions."

As stated in Chapter III, there are also important cortical centers for autonomic control located in the mesial and inferior surfaces of the frontal lobe. When the anterior limbic portion of the cingulate gyrus was stimulated by W. K Smith (1945), he obtained pupillary dilatation, piloerection, and cardiovascular responses—both excitation and inhibition, depending on the point of stimulation Similar responses have been obtained in man by Pool and Ransohoff (1949), who stimulated this area in the course of topectomy. On slow, 10-per-second stimulation of the posterior orbital surface of the frontal lobe, R. B. Livingston *et al.* (1948) and Chapman and the Livingstons (1949) found that there is arrest of respiration as well as a rise in blood pressure. As Chapman (1950) has suggested, it remains to be proved that these circulatory and respiratory responses obtained from electrical stimulation of the cerebral cortex are not merely pain reflexes transmitted by the sensory fibers

* Hoff, E C, and Green, H D. "Cardiovascular reactions induced by electrical stimulation of the cerebral cortex" *Amer J Physiol.*, 1936, 117: 411–422, courtesy of American Physiological Society, Inc, Washington

in the dura and cerebral vessels. On stimulation of the posterior orbital gyri in monkeys, the region of the anterior perforated area has been found by Sachs, Brendler, and Fulton (1949) to contain important areas concerned with visceral control. Appropriate stimulation of this area may lead to changes in blood pressure (predominantly elevation) and respiratory arrest, as well as dilatation of the pupil, salivation, and lachrimation.

In concluding this section on autonomic representation in the human cortex, brief mention should be made of the rare acute hemorrhages and perforations of the esophagus, stomach, and duodenum that may occur as fatal complications after head injuries and intracranial operations. First discussed by Cushing in his Balfour Lecture (1932), the subject has been restudied by Strassman (1947) and by Wyatt and Khoo (1949). Although the primary lesions usually involved the cortex and white matter, it seems likely that underlying autonomic centers must have been stimulated, but whether these were primarily hypothalamic or cortical remains uncertain. Sweet *et al.* (1948) have reported that, in addition to hemorrhage and perforation, profound biochemical disturbances may follow operations to the frontal lobes. These include extraordinary elevations of the blood sugar, nitrogen, chloride, and sodium levels. In their most striking case, serial sections of the entire brain disclosed no lesions other than the leukotomy incisions in the frontal lobes.

Autonomic Representation in the Cerebellum. The cerebellum, long considered the domain of somatic function alone, has recently been found to play a part in the regulation of respiratory and circulatory activity through its action on the autonomic centers in the underlying medulla. Moruzzi (1940) has shown that weak faradic stimulation of the paleocerebellar cortex (anterior lobe) causes strong inhibition not only of decerebrate rigidity, as is well known, but also of vasomotor reflexes and of the respiratory center. Connor (1941) has demonstrated, furthermore, that ablation of this area reduces the efficiency of thermal regulation.

The Central Ganglia in the Diencephalon. Recent investigations from many diverse angles have contributed to knowledge of the function of the central autonomic nuclei. To make the story of this research complete, we must go back to the work of Goltz forty years ago (1892). This showed that the decorticated dog is subject to manifestations of rage accompanied by signs of intense activity of the sympathetic nervous system. Dusser de Barenne (1919) made similar observations on cats, and Bard's (1939) extensive investigations have shown that the sham-rage

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rate identical with the integrated response of the animal to an elevated environmental temperature. Of pathological interest is the fact that Morgan and Vonderahe (1939) have found cellular degeneration in this exact area after death from heat stroke.

Interesting human cases of disturbed temperature regulation have been observed in the presence of tumors invading or compressing the hypothalamic nuclei. Davison and Freidman (1937) have described a newborn infant with hydrocephalus whose body temperature fluctuated from 93 to 103° F (33.5 to 39° C) throughout the four weeks' course of its life. At post-mortem, in addition to generalized dilatation of the ventricles, most of the hypothalamic nuclei were found to be destroyed by an infiltrating neuroblastoma. A second patient, thirty-one years old, with mild diabetes insipidus, adiposogenital dystrophy, hypersomnia, and prolonged subnormal temperature, was studied by Davison and Selby (1935). For the last three months of his life the temperature had ranged from below 90 to 96.6° F (33 to 35° C). In this instance an angioma situated in the floor of the third ventricle had partially destroyed the rostral portions of the supraoptic and paraventricular nuclei, together with the right mammillary body.

Posterior hypothalamic lesions produced experimentally in animals are often followed by striking somnolence. Ranson and Magoun (1939) have postulated that this region contains a "waking center." Corroborative evidence in favor of this theory has been brought forward by Serota (1939) and Harrison (1940) and the work of W. R. Hess (1948). Globus (1940) has reported states of protracted somnolence in two patients with verified bilateral lesions in this area. Other cases have been described by Davison and Demuth (1945).

Evidence for parasympathetic representation within the hypothalamus was reported by Beattie (1932). On stimulating the lateral wall of the infundibulum under light barbital anesthesia, he observed an increase in gastric peristalsis and secretion, hyperemia of the gastric mucosa, bradycardia, and increased peristalsis with a rise in bladder tone. Beattie therefore postulated that the preoptic region and anterior hypothalamus controlled the parasympathetic nervous system. Beattie and Sheehan (1934) also found pupillary constriction, fall in blood pressure, and rise in intragastric pressure, with increased peristalsis of the stomach, as a result of stimulation in this area. Stavraky (1936) was able to obtain in addition a dilatation of the pial arteries. As summarized by Ranson and Magoun (1939), stimulation of the preoptic area just in front of the optic chiasm and beneath the anterior commissure may cause contraction of the bladder,

phenomenon is due to release of the sympathetic centers in the hypothalamus after removal of cortical inhibition. The part of the frontal lobes which is primarily responsible for hypothalamic inhibition appears to be the rhinencephalon and medial orbital gyri (area 14), as Bard and Mountcastle (1948) have produced sham rage in cats and monkeys by lesions limited to these areas. Although the phenomenon has not been encountered in man as a result of injury localized to this area, it has been reported by Wortis and Maurer (1942) following diffuse cortical destruction from severe insulin hypoglycemia and carbon monoxide poisoning.

In 1909 Karplus and Kreidl began their investigation of the higher autonomic centers in the diencephalon by electrical stimulation of the walls of the third ventricle. Their investigations have been summarized by Karplus (1937). The position of the nuclear masses in this area has been established with a fair degree of accuracy (see p. 20), and much has been learned about their function by localized stimulation and destruction. This work has been facilitated by the Horsley-Clarke stereotaxic instrument, and a number of excellent papers have appeared on the subject. The investigations of Ranson and his school, who have been the most assiduous workers, have been reviewed by Ranson and Magoun (1939). Another summary of outstanding interest, particularly of work in England, has been published by Beattie (1938). Further papers of special value by American investigators are collected in the publications of the Association for Research in Nervous and Mental Disease (1940) and Magoun's more recent summary (1943). The reader who is interested in this work can obtain a comprehensive review and an extensive bibliography from these sources.

For the purpose of this surgical monograph the role of the hypothalamic centers must be reviewed in a concise and rather dogmatic form. In brief, very clear evidence has been presented that stimulation of the paraventricular nuclei and the walls of the third ventricle more posteriorly results in a widespread discharge of the sympathetic division. Nearly all of the characteristic responses, such as rise in blood pressure, cardiac acceleration, pupillary dilatation, erection of hairs, etc., have been produced by local stimulation of this area. Destruction of the same region has resulted in inability of animals to maintain their body temperature, but when the injury is more anteriorly situated, instead of poikilothermism, there follows hyperthermia from inability of the organism to get rid of excess heat. Conversely, heating the region of the preoptic nucleus, carried out by Beaton and his coworkers (1943*A* and *B*) in Ranson's laboratory, produced vasodilatation and sweating, with an increase in respiratory

because he found that, in rats whose spinal cords had been severed in the upper thoracic region some weeks previously, painful stimuli above the level of transection failed to bring about any drop in the eosinophil count. He therefore concluded that the only hypothalamic centers associated with ACTH release in the normal animal are those that have already been identified as responsible for the reflex secretion of epinephrine.

Cleveland and Davis (1936) have also shown that the hypothalamus may influence the secretion of diabetic hormone from the anterior pituitary. These investigators report that bilateral lesions of the tuber cinereum at the level of the ventromedial hypothalamic nuclei may be followed by pancreatectomy without the development of hyperglycemia and glycosuria. Such animals also become hypersensitive to insulin. In other words, injury to hypothalamic centers seems to produce the same effect as removal of the anterior lobe of the pituitary.

Other hypothalamic responses of clinical importance are the control of food intake (Brobeck, Tepperman, and Long, 1943; Cox, 1946) and obesity (Hetherington, 1943).

Responses observed in the course of operations on the third ventricle in man have been reported by one of us (White, 1940*A*) and confirm the conclusions which have been derived from animal experiments. In the course of opening the lamina terminalis (the anterior wall of the third ventricle) for drainage of hydrocephalus in 5 adult patients under local anesthesia, it was possible to observe the effects of electrical stimulation of the region of the paraventricular nuclei. In each case there was a sudden and dramatic acceleration of the heart and a rise in blood pressure (Fig. 22). The maximum acceleration of the pulse was from a basal rate of 55 to 145 beats per minute, with an elevation in systolic blood pressure of 20 mm. The change occurred after a latent period of two seconds and lasted for two minutes after the current was cut off. As in experimental animals, electrical stimulation in the preoptic region was less effective in eliciting a parasympathetic response. A slowing of the heart from 52 to 45 is shown in Figure 22, but even this slight degree of bradycardia was not consistently obtained.* On the other hand, operative manipulation of the anterior hypothalamus consistently produced a sudden reflex bradycardia with a maximum slowing of the heart from an initial rate of 175 to 70 beats per minute. Loud gastric peristalsis, nausea, and vomiting occurred in one instance, and abrupt loss of consciousness in 4 of 8 patients. Similar observations

* It is quite possible that a more definite bradycardia could be obtained on electrical stimulation, were it not for the extreme slowing already induced by operative manipulation of the anterior hypothalamus. Slowing of the heart on manipulation above the chiasm does not occur when atropine and ether anesthesia are used.

inhibition of respiration, and sometimes moderate falls in blood pressure.

A third important function of the hypothalamus is the control of the pituitary gland. There is satisfactory proof that it controls secretion of the posterior lobe. This has been investigated by Fisher, Ingram, and Ranson (1938), and the results of their experiments, together with the extensive literature on the subject, have been brought together in a monograph. By means of the supraopticohypophyseal tract, the hypothalamus regulates the secretion of antidiuretic hormone from the pars nervosa of the pituitary. Further confirmatory evidence has recently been reported by G. W. Harris (1947) from stimulation of the tract, and by Pickford (1947) from the application of acetylcholine to the supraoptic nucleus; also by Dandy's (1940) observation of development of diabetes insipidus in a patient after he had cut the pituitary stalk. When either the nervous pathway or the posterior lobe is injured, polyuria results. This confirms and extends the theory, first promulgated by Hann (1918), that diabetes insipidus occurs in the absence of the neural division if there is pars anterior tissue present.

Proof that anterior lobe secretion is regulated by the hypothalamus is far less impressive. The most convincing evidence is the work of Uotila (1939) on the activity of the thyroid during exposure to cold. Under these circumstances there is increase of thyroid secretion which is mediated by the thyrotropic hormone. This, in turn, appears to be stimulated by impulses transmitted from the hypothalamus through the pituitary stalk, because it fails to occur after stalk transection.

Hume and Wittenstein (1950) have found that adrenocorticotropic hormone is produced during stress by stimulation of the hypothalamus (afferent nerve impulses, epinephrine, insulin, and other hormones). Release of ACTH from the anterior lobe of the pituitary, which, in turn, affects the adrenal cortex and thereby produces the normal eosinopenic response, can be abolished in dogs by making small electrolytic lesions in the hypothalamus. Similarly, the barbiturates, which have an inhibitory effect on the hypothalamic nuclei, also decrease the eosinopenic response that follows trauma in the normal animal. Since hypothalamic control of ACTH release from the pituitary is not abolished by cutting the pituitary stalk, it must be mediated by a humoral mechanism through the circulation rather than through direct nervous connections, as is the case with release of antidiuretic hormone from the posterior lobe. Because complete sympathectomy does not alter the response, these authors concluded that neither epinephrine nor sympathetic fibers to the pituitary are essential to the stress phenomenon. Exception to these findings has been taken by Long (1950)

third ventricle frequently destroy the heat-regulating mechanism (Peet and Kahn, 1936; Alpers, 1936; Davison, 1940). Peet and Kahn reported on a patient with a hypothalamic tumor who developed severe vasoconstriction with cyanosis and sweating of the extremities, simulating Raynaud's syndrome. Other sequelae which have been observed in man include psychic changes (Gagel, 1936; Alpers, 1940), abnormal somnolence (von Economo, 1926 and 1930; Globus, 1940), and diabetes insipidus (Bailey, 1940). In the case of a woman with a pedunculated tumor in the third ventricle reported by Penfield (1929), extraordinary outbursts of autonomic activity appeared in repeated attacks. These manifestations consisted of cutaneous vasodilatation, salivation, sweating, and pilomotor activity. Tears flowed from both eyes, the pupils dilated, and in severe attacks the eyeballs protruded. The heartbeat became strong and rapid, while the respiration was slowed. Following an attack, the patient became constipated and experienced difficulty in emptying her bladder. She finally died after a prolonged series of attacks. Post-mortem examination revealed a cholesteatoma of the choroid plexus which protruded into the foramina of Monro, causing an internal hydrocephalus. A second and closely similar case, resulting from an astroblastoma which arose from the floor of the third ventricle, has been reported by McLean (1934). More recently, Urechia (1949) has contributed 5 additional cases of epileptiform diencephalic crises in individuals with mild Parkinson's disease and associated oculogyric crises. Urechia believes that these attacks, consisting of tachycardia, sweating, vasomotor changes, and a feeling of great emotional tension, are a form of epilepsy which begins in the hypothalamus and does not spread to cortical areas.

Alvarez (1940), who has made a long study of the complaints of nervous individuals, points out that many of their symptoms are in reality disconcerting tricks played on the heart, blood vessels, digestive tract, kidneys, and skin by an overirritable involuntary nervous system. In health, visceral function is regulated so well by the autonomic nuclei in the hypothalamus that the normal individual is nearly unconscious of his internal organs. As Bard's work (1939) has shown, this regulating center is normally kept in check by the cerebral cortex, but, when upset in any way, it may work erratically and thereby cause disagreeable symptoms in many organs of the body, viz., palpitation, vasomotor disturbances, insomnia, and many varieties of gastrointestinal disorders, endocrine dysfunction, etc. Alvarez presents convincing evidence that the hypothalamus can be upset by fatigue, lack of sleep, or nervous strain; that in many persons it behaves erratically because of bad nervous inheritance; and that it may also be injured by an

have often been made in the course of operative manipulation in this area (Dott, 1938). These responses, however, could be equally well explained on the basis of compression of area 13 in retraction of the frontal lobe, as the posterior orbital gyrus plays such an important role in the regulation of visceral activity.

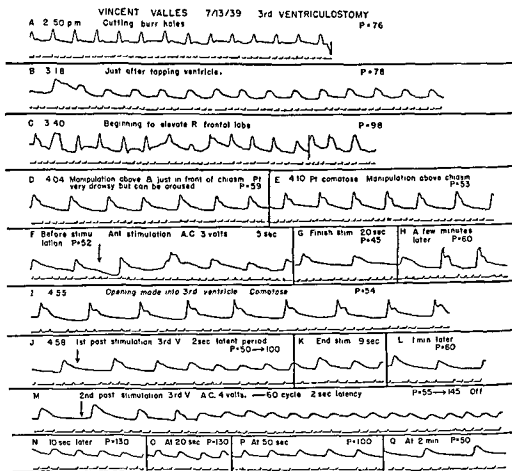


Fig. 22. Changes in heart rate and blood pressure which accompany stimulation of hypothalamic nuclei in man.

D. and E Operative manipulation above optic chiasm
F. and G. Electrical stimulation in region of anterior commissure
J. and M Electrical stimulation of lateral wall of third ventricle in region of paraventricular nucleus

(Reproduced from White, J. C. "Autonomic discharge from stimulation of the hypothalamus in man." *Res. Publ Ass nerv. ment Dis*, 1940, **20:** 854–863, courtesy of *Williams and Wilkins, Baltimore.)*

In addition to these direct observations on the human hypothalamus, there are numerous clinical observations which point in the same direction. Tumors and other lesions which compress or destroy the walls of the

medulla in 2 cases of respiratory failure, indicate that this localization of the respiratory centers in the cat may be applied roughly to man.

It was formerly supposed that nuclei in the medulla exert an important influence on the metabolism and heat-regulating mechanisms, but recent work has placed these centers at higher levels in the brain. Claude Bernard (1852) produced glycosuria by his classical puncture of the floor of the fourth ventricle, but the probable explanation of this effect is that he injured conduction pathways from the hypothalamus. There is evidence that carbohydrate metabolism is governed by the pituitary diencephalic mechanism (see p. 69), and it is most likely that the general metabolic control of the body is also situated in the higher centers of the diencephalon.

Autonomic Centers in the Spinal Cord. As described at the beginning of this chapter, the character of the autonomic functions, as well as the anatomical arrangement of the sympathetic nerves, necessitates a widespread distribution of their discharge. This is particularly widespread in the case of the vasomotor outflow. In the human upper extremity, Ray, Hinsey, and Geohegan (1943) have shown that stimulation of any anterior root from T2 to T10 will produce a change in the electrical resistance of the skin over the entire hand. In patients with Raynaud's disease, division of all but one of the anterior roots which carry preganglionic vasoconstrictor fibers resulted in the preservation of much of the sympathetic activity in all parts of the hand. In contrast, the nerve supply of individual organs is given off from more localized areas in the thoracolumbar and sacral regions of the spinal cord. Present knowledge of segmental levels is summarized in Table I.

After complete destruction of the lower spinal cord, all regional reflex activity, visceral as well as somatic, is abolished. Bolton, Williams, and Carmichael (1937) have found that all vasomotor reflexes in the lower extremities are then abolished. On the other hand, when the upper cord has been transected, but reflex activity has recovered in the lower isolated segments, uninhibited reflex activity may be increased in smooth as well as striated muscle. This is clearly shown in the cystometrogram in cases of chronic spastic paraplegia by the forceful contractions of the bladder in response to stretching of its walls (F. C. McLellan, 1939) and, similarly, by recording pressure changes on distention of the rectum and lower colon (White, Verlot, and Ehrentheil, 1940). Spinal autonomic reflex activity accounts for the recovery of autonomous control of the bladder and colon in individuals with spastic paraplegia, and also for a number of other disturbances such as segmental sweating on distention of the bladder, piloerection, penile erection, and seminal emission (Kuhn, 1950).

encephalitic virus or in older persons by little thromboses due to arteriosclerosis.

In summary, the hypothalamus, in addition to carrying out the expression of emotion, serves as a regulator of body temperature, the sleep-waking rhythm, metabolic exchange, and the whole delicate involuntary adjustment to the external environment. Through its influence on the pituitary body, as yet but poorly understood, it enters into the control of the endocrine system. In addition, through its nervous connections with the cerebral cortex and the thalamus, it is the recipient of those vague and indefinable stimuli which arise in association with all sorts of visceral activities and metabolic processes. In this way it mediates the integration of visceral and psychic impulses, and plays an essential part in the control of the internal milieu of the organism.

Autonomic Centers in the Medulla Oblongata. While the highest regulatory centers lie in the diencephalon, other important reflex centers governing vegetative processes are situated in the medulla. The important autonomic nuclei which contribute fibers to the cranial nerves are shown in Figure 6. As has been pointed out in Chapter III, the respiratory and vasomotor centers are closely associated with the dorsal motor nucleus of the vagus. It has long been known that when the brain stem is gradually sliced away, no fall in blood pressure is produced until the middle of the pons is transected, and that lower sections result in still greater drops in blood pressure until a point is reached just above the lower end of the fourth ventricle. No more exact delimitation of this area was made until the investigation of Ranson and Billingsley (1916*A*). Their stimulation experiments suggest that there is a vasopressor center at the apex of the ala cinerea or the fovea inferior and a depressor point slightly caudal to this (in the area postrema just lateral to the obex). Regardless of whether there are separate vasoconstrictor and vasodilator centers, it is certain that a well-located bulbar area controls the sympathetic outflow to the arterioles, and that its tonic activity may be increased or decreased by afferent nerve impulses or by variations in the blood supply (Bard, 1929).

Another important area in the medulla which is situated more deeply in the reticular formation controls the rate and depth of respiration. This also has been divided into two opposed centers by Pitts, Magoun, and Ranson (1939*A*). Stimulation of the more caudal area, which overlies the cephalic four-fifths of the inferior olive, results in maximum inspiratory movements of the thorax and diaphragm. Cupped over the cephalic end of the inspiratory area is a region from which expiratory movements are obtained. Figures presented by Finley (1931), showing lesions in the

SUBSIDIARY REFLEX CENTERS THAT MODIFY THE ACTIVITY OF THE AUTONOMIC NERVOUS SYSTEM

a. The Carotid Sinus Mechanism.

The role of the carotid sinus as a secondary mechanism in the control of cardiovascular and respiratory activity was first pointed out by Hering in 1923. The physiological importance of the sinus nerves has been summarized in his book (1932) and greatly expanded by the work of Heymans and his collaborators in Ghent. They point out that there is a peculiar innervation of the region in which the common carotid divides into its internal and external branches; from this bifurcation a number of afferent rami are given off to the vagus and glossopharyngeal nerves. Stimulation of these fibers gives rise to far-reaching reflex responses (Fig. 13). The following is a summary of this work, which was described in a monograph by Heymans, Bouckaert, and Regniers (1933).

Carotid sinus regulation of blood pressure: At normal arterial pressure, variations of tension of only 10 to 20 mm of water in the carotid sinus produce marked fluctuations in general systemic blood pressure. When the carotid sinus pressure is raised, the systemic pressure falls. At pressures above 200 mm and below 50 mm of mercury, reflex control of vasomotor tone disappears. The authors have demonstrated that within these limits a rise in carotid pressure will produce peripheral vasodilatation and a fall in general systemic blood pressure. There is also an increase in the size of the spleen and of the intestines, together with a diminution in rate of blood flow and an increase in cardiac volume.

Reflex regulation of the heart and lungs by the carotid sinus: Heymans has also shown that the carotid sinus exerts an important reflex control on the activity of the heart and lungs. Perfusing the carotid sinus with blood containing varying concentrations of carbon dioxide and other weak acids causes characteristic acceleration of respiration, even though the blood flowing through the brain is unaltered. In the case of the heart, marked changes in its rate and the force of its beat can be produced by perfusing the isolated carotid sinus with adrenaline.

Bronk (1931) has further elaborated Heymans' studies. By using a vacuum-tube amplifier and an oscillograph attached to the carotid sinus nerve, he has been able to show a burst of nerve impulses accompanying each heart cycle. This discharge is coincident with the rapid rise in arterial pressure revealed by the carotid pulse curve. At high blood pressures this discharge becomes continuous, an effect which is also produced as the result of asphyxia. The general character of these discharges from the

TABLE I

The Segmental Motor Innervation of the Viscera

Organ	*Segments Which Give Off Parasympathetic Neurons*			*Segments Which Give Off Sympathetic Neurons*													
				Thoracic												Lumbar	
	Higher cranial segments	Vagus nerve	Second to fourth sacral nerves	1	2	3	4	5	6	7	8	9	10	11	12	L1	L2
Eyes	+			+	+	+	+										
Salivary glands	+			+	+	?											
Blood vessels of meninges and brain	+			+	+	?											
Blood vessels of head and neck				?	+	+	+										
Sweat glands of head	+			?	+	+	+										
Blood vessels, sweat glands, and erector pili muscles of arms				?	+	+	+	+	+	+	+	+	+				
Heart		+		+	+	+	+	?									
Lungs		+			+	+	+	+	+	+							
Esophagus, stomach, liver, pancreas, and small intestine		+						+	+	+	+	+	+	+			
Adrenal													?	+	+	+	?
Kidney		?												?	+	+	?
Bladder			+													+	+
Genitalia			+													+	+
Colon and rectum			+													+	+
Blood vessels, sweat glands, and erector pili muscles of legs														+	+	+	+

greater than the total volume of the blood, active vasoconstriction must be in force over large areas to ensure an adequate circulation to the vital organs. When an unusual demand for blood arises in a given territory, it may be met either by a relaxation of vasoconstrictor tone or by active vasodilatation. As the problem of modifying deficient circulation in the extremities is of primary concern to the surgeon, this phase of vasomotor physiology requires particular emphasis.

The most common vasoconstrictor is cold. As Maddock and Coller (1933) have pointed out, vasomotor reactions are most intense in the extremities. The arms and legs comprise 65 per cent of the body surface and, by their efficient vasomotor responses, regulate in major part the elimination or storage of body heat. Under such conditions as pain, fear, anger, asphyxia, hemorrhage, and dehydration, vasoconstriction in the extremities may become so intense that the cutaneous circulation nearly comes to a standstill. In certain abnormal states, chronic vasospasm may persist in normal surroundings and may produce a degree of stasis in the terminal arterioles that causes color changes, pain, and eventually trophic disturbances. Attempts to relieve vasospasm by section of the vasoconstrictor nerves constitute one of the most interesting chapters in the field of sympathetic neurosurgery.

Knowledge of the segmental level of the vasoconstrictor outflow has been worked out by animal experiments and observations on man. Budge (1853) discovered that hemisection of the cord at the last cervical segment resulted in a striking increase in temperature of the rabbit's ear on the side operated upon. Edes (1869) later observed that the vasomotor fibers to the arm leave the spinal cord as low down as the sixth thoracic segment. According to Langley's well-known findings (1892), which were derived from stimulating the motor roots within the spinal canal, vasoconstrictor, as well as sudomotor and pilomotor, impulses to the arm are given off from the fourth to tenth thoracic segments in the cat. In analyzing these findings with the advantage of more recently acquired knowledge, it is evident that higher segments give off vasoconstrictor fibers to the arm. Sheehan and Marrazzi (1941) have repeated Langley's experiment, using the cathode-ray oscillograph to detect sympathetic impulses in the peripheral nerves of the arm and leg. With this sensitive indicator they have found that the fourth to eighth thoracic segments contribute sympathetic fibers to the arm. This work was done on monkeys. In man, an even greater number of segments contributes vasoconstrictor and sudomotor fibers. Foerster (1939) has stimulated ventral spinal roots on the operating table and made the following observations: Stimulation of the

carotid sinus agrees closely with those found in the cardiac depressor nerve. The activity of the sensory nerve endings in both areas appears to constitute an important mechanism in preventing excessively high blood pressure or dangerously rapid heart rates.

b. The Cardiovascular Depressor Mechanism in the Aortic Arch.

Still another secondary mechanism for the control of the heart and blood vessels lies in the sensory network in the arch of the aorta. From this plexus impulses reach the higher cardiovascular centers over the depressor branch of the vagus, the nerve of Cyon and Ludwig (1866). These afferent impulses set up cardio-inhibitory and vasodilator responses and protect the organism from sudden and dangerous periods of hypertension. Like the carotid sinus mechanism, the sensory zone in the aortic arch modifies the general activity of the autonomic system in a reflex manner.

Axon Reflexes. The lowest level at which segmental adjustments of general visceral activity take place lies in the sympathetic ganglia. Although anatomical evidence is lacking to show synapses between visceral afferent and motor neurons outside the spinal cord, some physiological evidence exists that reflex actions may, under certain circumstances, be carried out through the sympathetic ganglia (Kuntz, 1940 and 1945). Sokownin (1874) first observed this response in the inferior mesenteric ganglion. After severing all central connections, stimulation of the central end of one hypogastric nerve resulted in contraction of the bladder from an efferent impulse descending the other nerve. Langley and Anderson (1894) reproduced this response and observed at the same time a contraction of the internal anal sphincter and blanching of the mucous membrane of the rectum. These reflexes were blocked by nicotine applied to the inferior mesenteric ganglia. Since these reactions were unlike the ordinary spinal reflexes, Langley (1900*A*) called them pseudo or axon reflexes. He also noted that reflex impulses traversing a preganglionic neuron usually spread over three to four segments, whereas a postganglionic reflex, carried out through a single axon and its branches, called forth a response limited to its own proper distribution. The whole subject of axon reflexes is somewhat obscure and should be reinvestigated with modern physiological methods.

III. Visceral Responses to Autonomic Stimuli

Vasoconstriction. In addition to distributing vasoconstrictor fibers to the entire surface of the body, the sympathetic system constricts the cerebral and retinal arteries, as well as the great vascular network to the splanchnic and pelvic viscera Since the capacity of the vascular bed is

greater than the total volume of the blood, active vasoconstriction must be in force over large areas to ensure an adequate circulation to the vital organs. When an unusual demand for blood arises in a given territory, it may be met either by a relaxation of vasoconstrictor tone or by active vasodilatation. As the problem of modifying deficient circulation in the extremities is of primary concern to the surgeon, this phase of vasomotor physiology requires particular emphasis.

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first and second thoracic motor roots produced vasoconstriction of the ipsilateral face and neck, but no vasomotor changes in the arm; stimulation of the third to seventh ventral roots caused plethysmographic evidence of vasoconstriction in the upper extremity.

By the more sensitive methods of observing pupillary changes and reduction in the electrical resistance of the skin, Ray, Hinsey, and Geohegan (1943) have proved that the sympathetic outflow is even more widespread. Pupillary dilatation could be obtained from stimulating the third and fourth as well as the two upper thoracic roots, and, in 1 of 10 subjects tested, a response was obtained from C8. Reduction in electrical skin resistance of the upper extremity was observed from segments as low as T10, and in one case a response was obtained from stimulation of the first thoracic root on one side, though not from the other. This gives support to the claims of Kuntz (1949) that sympathetic denervation of the upper extremity is not likely to be complete unless the first thoracic white ramus is divided. The impulses that leave the first thoracic root are certainly not sufficient to give any detectable response except by the more refined methods of testing, but they may well become more important with time and the development of sensitivity in the partially denervated smooth muscle of the arterioles. Incomplete interruption of the sympathetic vasoconstrictor outflow has been one of the causes of failure in the surgical treatment of Raynaud's disease of the upper extremities (see Chap. VIII).

Langley (1891*A* and *B*) also studied the sympathetic outflow to the hind limbs of the cat and concluded that these impulses originate from the eleventh thoracic to second lumbar levels. Sheehan and Marrazzi (1941) have found that, in the monkey, fibers arise from the twelfth thoracic to third lumbar segments. These correspond in man with the eleventh thoracic to second lumbar roots, which evidence from direct stimulation has shown to carry the sympathetic impulses to the lower extremity..

While the most active vasoconstriction takes place in the arterioles, a definite nervous control of the capillaries and veins has also been demonstrated Beecher (1936), working in Krogh's laboratory, studied the capillaries in the rabbit's ear with the Clark window technique. He observed that cessation of flow through the capillary loop results from constriction of the Rouget cells and swelling of the endothelial cell nuclei This reaction follows disagreeable stimuli within a second, too short a latent period for anything but nervous action. More recent direct measurements of capillary blood pressure have been made by Eichna (1943). They indicate that, after sympathectomy in Raynaud's disease, there is a strik-

ing rise of pressure in the arteriolar limb (9.3 mm mercury), and a more favorable pressure gradient is established. The abnormal capillaries, with a slowly flowing, bluish-red blood, become smaller and narrower, with increased rate of flow and better oxygenation of the blood. This change Eichna attributes not to removal of capillary innervation per se but to the improvement in digital circulation which follows the abolition of periods of circulatory arrest.

Evidence that the veins are also under the control of the nervous system has been summarized by McDowall, Malcolmson, and McWhan's (1938) monograph on the control of the circulation. They cite the experiments of Gollwitzer-Meier and Bohn (1930), who found that the mesenteric veins of dogs, when connected to the animal only by the nerves, are constricted when carbon dioxide is inhaled. There is further evidence that venous tone can be increased or inhibited reflexly as the result of pressure changes in the carotid sinus. The fact that the veins become engorged after sympathectomy is therefore not entirely due to the *vis a tergo* of an increased blood flow through the capillaries but is in part due to their release from the vasoconstrictor center.

Vasodilatation. Although a concise knowledge of the vasodilator mechanism is still lacking, it is known that generalized vascular relaxation can be brought about by both sympathetic and parasympathetic impulses. Dale's (1906) discovery that adrenaline, after paralysis of the sympathetic constrictor effects by ergotoxine, causes a fall instead of a rise in pressure is perhaps the best evidence for a separate system of sympathetic vasodilator nerves.

It was formerly believed that vasodilator fibers run in the sympathetic outflow to the extremities, because of T. Lewis and Pickering's (1931) demonstration that the sympathectomized extremity fails to attain as high a cutaneous temperature as the normal control in response to heating the rest of the body. Sarnoff and Simeone (1947), who investigated this problem with greater care, found that this failure to attain maximal vasodilatation cannot be caused by paralysis of hypothetical sympathetic vasodilator fibers, because when, under similar circumstances, an extremity is acutely denervated by procaine block, it does not cool but becomes even warmer than the control side. Indirect vasodilatation of an extremity, produced by heating other areas of the body, must therefore be due solely to central inhibition of vasoconstrictor fibers, and the failure of the chronically sympathectomized extremity to warm as much as the normal control side must be ascribed to other factors which come into play secondary to degeneration of nerve fibers.

In certain special tissues the usual vasoconstrictor role of the sympathetic fibers is reversed, and the reaction to their discharge as well as the reaction to adrenaline is vasodilatation. This appears to be the case with the coronary (see p. 84) and pulmonary * arteries.

It has long been recognized that parasympathetic dilator fibers run to the upper abdominal viscera in the vagus and to the pelvic organs in the sacral nerves. Parasympathetic dilator fibers also run in the sensory portion of the facial (nervus intermedius of Wrisberg), to the lachrymal and salivary glands (p. 41), to the tongue (p. 246), and to the cerebral vessels (p. 42).

Considerable obscurity still persists concerning the anatomical distribution of the vasodilator fibers to the peripheral vascular system over posterior spinal roots. S. Stricker (1877*B*) first demonstrated flushing in the extremities by stimulating the distal ends of the divided posterior spinal nerve roots. Bayliss (1901), who repeated Stricker's experiments, found that these fibers do not join the sympathetic chains and do not degenerate when the posterior roots are cut; hence, he concluded that their trophic cells must lie in the sensory root ganglia, and that the vasodilator fibers are, in fact, identical with the sensory afferent neurons. Consequently, he postulated an "antidromic" type of conduction, which necessitates the assumption that the sensory neurons may transmit impulses in a direction contrary to that stipulated in the Bell-Magendie Law. A heated discussion has arisen over the problem whether the vasodilator action of the posterior roots may be transmitted over a special set of efferent fibers (Foerster, 1928; Kuré, 1931; Barron and Matthews, 1935; Sheehan, 1935; Okelberry, 1935), or whether the intact fibers which have been observed in the central stumps of cut posterior roots represent regenerating axons which have bridged the gap between the severed root endings by regeneration from the distal stump (Ranson, 1914; Hinsey, 1934; Westbrook and Tower, 1940). Sheehan (1935) summarized the status of this difficult problem by saying that it "unfortunately does not allow of a final histological solution, as the times for regeneration and degeneration overlap, and it is almost impossible to fix an arbitrary time at which one can be sure that all requisite degeneration has taken place and no regeneration has occurred." It is possible, as Sheehan has suggested, that vasodilatation is mediated over posterior roots by a special set of fibers with their cell bodies in the root ganglia, and that they are ordinarily stimulated through afferent impulses over the sensory fibers as a form of axon reflex. After evaluating the evidence given above, we have been forced to conclude that it is most un-

* For the lung, this has been conclusively established only in cold-blooded animals

likely that the cell bodies of these fibers lie in the spinal cord, and that there is no reason whatever to believe that they belong to the parasympathetic system, as was proposed by Kuré (1931).

Vasomotor Responses in Skeletal Muscle. Present concepts of the physiological mechanism that controls the flow of blood in skeletal muscle are extremely confused because of extraordinary variations in different species of animals which have been used for investigation (Burn, 1938). In experimenting on dogs, Roome (1938) has observed that adrenaline causes a combined dilatation and constriction in the muscles. He suggests that the local action of this drug on the blood vessels in striated muscle causes dilatation of the capillaries but constriction of the arterioles. In man, R. T. Grant (1938) found that the local vascular effects of exercise are independent of the sympathetic nerves, and evidence points strongly to relatively stable metabolites as being responsible for the hyperemia of exercise. The action of nervous stimuli on the vascular bed of skeletal muscle has been extremely difficult to quantitate, but a fairly satisfactory approximation has been made by measuring volume changes in the extremities by a plethysmograph. This method, developed by Grant and Pearson (1938), compares the alterations in volume which occur in the hand or foot with those in the forearm and calf. In the more distal portions of the extremities, where the skin constitutes a large proportion of the total volume, the reaction to painful stimuli and to adrenaline is strongly vasoconstrictor. In the forearm and calf, however, where the greater bulk of tissue is composed of skeletal muscle, sensory stimuli have either no effect or produce vasodilatation.

H. Barcroft and Edholm (1946), by measuring forearm circulation with a special plethysmographic technique, observed that blood flow in acutely denervated muscles is more than doubled, but this increase is of short duration They concluded that release of vasoconstrictor tone may result in a small increase of about 1.5:1, whereas it is increased by chemical metabolites in strenuous exercise at a rate of nearly 20:1.

These findings fit in with the clinical observation that intermittent claudication from impairment of circulation in the leg muscles in peripheral vascular disease may, in some cases, be improved by sympathectomy (see p. 203).

Piloerection. Erection of hairs diminishes radiation of body heat. It is solely under sympathetic control, there being no known parasympathetic inhibition. While this function is rudimentary in man, its distribution coincides with the nerve supply of the cutaneous vessels and sweat glands, and its loss is an important sign of sympathetic paralysis.

in animals, is nothing more than an optical illusion in man, due to the narrowed palpebral fissure. Müller's muscle, which protrudes the orbit in animals, is not developed in man, and measurements with the exophthalmometer by Mutch (1936) and Pochin (1939) have shown that there is no actual protrusion or recession of the human eyeball during stimulation or paralysis of the cervical sympathetic fibers. Further clinical changes associated with this phenomenon are described in Chapter X (p. 250).

Salivation. Both systems of nerves stimulate the secretion of saliva. Heidenhain (1868), who first investigated the neurogenic control of salivary secretion, showed that in the dog weak faradic stimulation of the chorda tympani nerve causes vasodilatation as well as a thin, copious, increased secretion of the submaxillary and sublingual glands. Stimulation of the cervical sympathetic also causes a slight amount of secretion, but this is thicker in quality and thirty to sixty times less than the amount obtained from a discharge of corresponding intensity over the chorda tympani. At the same time the glands show distinct vasoconstriction. Langley (1878) observed that when both the chorda tympani and cervical sympathetic nerves were stimulated, he obtained a more copious secretion than by stimulation of either nerve separately. These experiments show that autonomic impulses influence the flow of saliva by stimulating the secretory cells as well as by altering blood flow through the glands. From a clinical viewpoint it is fair to postulate that the cranial autonomic is the system chiefly responsible for salivary secretion.

Thyroid Secretion. This much-disputed subject has been reviewed by Means (1948). From the fact that Cannon, Binger, and Fitz (1915) succeeded in producing a syndrome very much like exophthalmic goiter in cats by anastomosing the phrenic nerve with the cervical sympathetic, it seemed at first as though thyroid secretion were stimulated by nerve impulses. But Friedgood and Cannon (1940), on the basis of more recent work, have concluded that this stimulation is probably a hormonal one secondary to stimulation of the anterior pituitary. Nonidez (1935), who has made the most careful study of thyroid innervation, draws the conclusion that there is no true secretory innervation, but that the gland's very complex vasomotor nerves may regulate the escape of hormone in the blood and may perhaps govern its production by regulation of the oxygen supply.

NEUROGENIC CONTROL OF THE THORACIC VISCERA

The antagonistic action between the sympathetic and parasympathetic systems is well exemplified in the response of the heart. Sympathetic stimula-

tion increases the activity of the cardiac musculature, resulting in an acceleration of the heartbeat and an increase in stroke output. In contrast to its general vasoconstrictor action, the sympathetic dilates the coronary arteries to supply the laboring heart muscle with an adequate flow of blood (Anrep and Segall, 1926; Gollwitzer-Meier and Krüger, 1935).* The vagus produces opposite motor effects. It also transmits afferent impulses from the arch of the aorta, which act on the cardiac and vasomotor centers in the medulla and bring about slowing of the heart rate and widespread vasodilator reflexes. In some animals, and occasionally in man, these fibers constitute a distinct branch (the depressor nerve of Cyon and Ludwig), but more commonly they ascend in the trunk of the vagus. The carotid sinus innervation is a further afferent reflex mechanism which serves to protect the heart from overexertion.

In the lung it is known that vagal stimulation constricts the larger bronchi, as this response has been observed through the bronchoscope. Beyond this it has been established that vagal receptor endings in the alveolar ducts play an important role in the reflex regulation of the respiratory cycle.

Little more has been conclusively proved concerning the vasomotor control of the pulmonary vessels than that they are adjusted to accommodate the output of the right ventricle. Bradford and Dean (1894) believed that their observations were an adequate demonstration of the existence of a vasomotor supply to the lungs, though they thought that this innervation was less well developed than that of the systemic vessels. A confused and contradictory body of publications on the subject has arisen since, but the balance of evidence is in favor of a weak vasomotor control. Hall (1923), by illuminating the surface of the lung, was able to study the behavior of the small vessels directly. He observed that the intravenous injection of adrenaline produced marked arteriolar constriction. Perfusion experiments on the isolated lung cited by Wright (1932) show that sympathetic stimulation causes definite vasoconstriction. DeBurgh Daly and von Euler (1932), who have made most carefully controlled experiments on lung innervation, found a rise in pulmonary artery pressure of 40 per cent on sympathetic stimulation. They also concluded that vasodilatation in the lung is probably due to vagal activity.

NEUROGENIC CONTROL OF THE DIGESTIVE TRACT

a. The Esophagus

Knight (1934) has reviewed the theories of esophageal innervation. In

* Not all investigators are in accord on this point, but we believe that the most satisfactory evidence favors this interpretation (see Chap. XI).

addition, he has presented interesting observations on the effect of stimulation or paralysis of the sympathetic and vagal branches to the esophagus. His experiments give clear-cut evidence that the vagus and splanchnic nerves exert an antagonistic influence on the tone of the esophageal musculature and its cardiac sphincter. In this dual mechanism, as in the case of the terminal gut, the parasympathetic stimulates peristalsis and constriction of the sphincter. Bilateral vagectomy in cats brought about a condition closely resembling cardiospasm in the human being. If allowed to continue, the animals died of obstruction, but if the sympathetic supply was divided by stripping the fibers surrounding the celiac axis, the condition of achalasia gave way to a patulous sphincter. Ferguson (1936) has produced cardiospasm in the same way, but attempts to relieve this condition in man by sympathectomy have not met with consistent success.

b. The Gastrointestinal Canal

Evidence that stimulation of the posterolateral nuclei of the hypothalamus (sympathetic centers) inhibits gastrointestinal activity and that stimulation more anteriorly causes an increase in gastric peristalsis and acid secretion has been presented. Sheehan (1940) has written the most complete review of this subject, and his article should be consulted by those who would seek further information and an extensive bibliography.

Although the smooth muscle of the stomach and small intestine, as well as the pyloric sphincter and the digestive glands, receives a dual innervation, separate stimulation of the splanchnic nerves or the vagi does not give any such clear-cut antagonistic response.

Cannon (1933), in his excellent review of the physiology of digestion, pointed out that some of the incongruous results obtained by electrical stimulation of the vagi and splanchnic nerves can be explained as a consequence of what he so aptly called "induction coil physiology." In the intact animal or human being, it is apparent during varying emotional states that the general autonomic influence on gastrointestinal activity follows the fundamental rules of homeostatic behavior. States of contentment and psychic stimulation at the sight or thought of food result in an active flow of gastric juice and a speeding up of the digestive processes.

The fact that the opposite disagreeable emotions can upset digestion has been recognized since the classical experiments of Beaumont (1833) on the fistulous stomach of Alexis St. Martin. He noted that violent passion was likely to cause a reflux of bile into the stomach, a change in the properties of the chyme, and a retardation of its passage onward into the intestine. Similar observations have been reported five times since by Richet (1878), Carlson (1912), Wolf and Wolff (1943*B*), and Andrus

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The recent studies connected with the physiological effects of vagotomy in the treatment of chronic peptic ulceration, summarized in Chapter XIII, have shown that while the secretory response to histamine and food in the stomach is chemical in nature, the vagi are primarily concerned with gastric motility and the activity of the mucosal glands during the early phase of psychic stimulation, as well as the continuous secretion that occurs in the resting stomach at night.

The physiological response to vagotomy is both motor and secretory. When all vagal connections with the stomach have been severed its motility is greatly reduced, and peristalsis no longer takes place in response to a sham meal, hunger, or insulin hypoglycemia. The total volume and acidity of secretion in the fasting stage, as well as that produced in response to insulin, are greatly reduced, at least temporarily. Free acid is often entirely absent.

Apart from the important role of the vagi in gastric motility and secretion, it is now generally recognized by gastroenterologists that the essential mechanisms that regulate these functions in the intestinal tract are mediated by the intrinsic nervous plexuses in conjunction with local chemical and hormonal stimuli.

In the lower portion of the sigmoid and rectum the characteristic clear-cut antagonism between the sympathetic and the sacral autonomic nerves again becomes apparent. Gaskell (1916) showed that the smooth muscle of the internal anal sphincter was contracted by the lumbar sympathetic nerves. Learmonth and Markowitz (1929 and 1930) made pressure readings in the rectosigmoid, demonstrating an increase in pressure on paralyzing the lumbar sympathetic fibers, and a fall in pressure on stimulating these same fibers. Adamson and Aird (1932) have been able to produce megacolon experimentally in cats by resecting the sacral autonomic nerves. There is therefore evidence that the thoracolumbar sympathetic outflow causes a relaxation of the muscle in the wall of the sigmoid and rectum with a coincident constriction of the internal sphincter, i.e., an inhibition of the defecation reflex. The sacral parasympathetic innervation, on the other hand, produces exactly the reverse effect and thereby stimulates defecation.

c. Liver and Pancreas

Claude Bernard (1877), after his discovery that glycosuria and hyperglycemia resulted from the puncture of a certain region in the floor of the fourth ventricle, studied the conduction pathways from this area to the liver. Following section of the spinal cord in the lower thoracic region, glycosuria resulted as before, but cutting the upper thoracic cord

(1947) on male subjects, and by Crider and Walker (1948) on a woman with a gastric fistula. The latter observed a moderately active secreting stomach with a red mucosa when their patient was fasting and in a happy, co-operative mood. Anger, resentment, fear, and anxiety were associated with decreased motility and secretion with blanching of the mucosa. The secretion at these times had a lower hydrochloric acid content. Heartburn, nausea, retching, and reflux of bile were caused by mechanical stimulation around the cardiac sphincter. The absence of hypersecretion and hypermotility in this subject at periods of sustained emotional tension was in striking contrast to the men who were previously studied. In the individual reported by Andrus, who was submitted to vagotomy, all irritable changes in the gastric mucosa which had been observed in response to emotion disappeared after the operation.

About a century ago the French philosopher and gourmet, Brillat-Savarin (1839), described the psychic stimulation aroused in contemplating savory food. "Memory recalls foods that have flattered its taste: imagination fancies that it sees them . . . the whole nutritive apparatus is moved. The stomach becomes sensible, the gastric juices displace themselves with noise, the mouth becomes moist and all the digestive powers are under arms, like soldiers awaiting the word of command. After a few moments there will be spasmodic motion, pain, and hunger." Indeed Alvarez (1929), from whom the preceding delightful quotation has been taken, cites another *bon vivant* (whose anal sphincters had been destroyed by a series of operations for fistula) in whom the sight, smell, or even the thought of food set up an uncontrollable defecation reflex. His rush waves of peristalsis were particularly annoying at breakfast, when his empty bowel was so sensitive that he had to eat seated on the toilet bowl.

The extrinsic nerves have much to do with digestive upsets associated with disease elsewhere in the body. Of interest in this connection are the studies of Walton, Moore, and Graham (1931) on the vomiting pathways of peritonitis. They have shown in dogs that both the vagus and the splanchnic nerves carry stimuli which lead to vomiting, and that both must be cut in order to prevent it. The splanchnics serve largely to quiet the tract and to stop digestion when the body is distressed or injured (Cannon, 1909). They solely transmit the sensations of pain on distention, in gastritis, and ulceration (see p. 370). It has long been known that the vagi carry feelings of hunger and satiety from the stomach to the brain; they help in adjusting the tone of the stomach to food coming down the esophagus (Cannon, 1911); and they carry stimuli that give rise to the psychic secretion of gastric juice (Pavlov, 1910).

The action of the extrinsic nerves on the digestive secretions of the pancreas is still not thoroughly settled. Although the secretion of water, bicarbonate, and the digestive enzymes in the pancreatic juice is stimulated in part by the action of secretin in the circulating blood, the digestive activity of the pancreas is also controlled by its autonomic nerves. Beginning in 1878, Pavlov observed that atropine inhibited pancreatic secretion. More recent experiments by his students show that the vagus nerves excite the pancreatic acini to secrete digestive juice. Mellanby (1926) has carried out the most complete studies on pancreatic secretion and found that as a result of vagus stimulation the trypsin and amylase in the pancreatic juice are increased, whereas the liquid and bicarbonate content remain unchanged. The secretion of the latter he ascribes to the action of secretin.

Mallet-Guy and his coworkers (1949) believe that stimulation of the left major splanchnic nerves, especially at the time of digestive activity, produces vasoconstriction followed by vasodilatation, edema, and histological changes suggestive of pancreatitis. They hypothecate that abnormal sympathetic activity in human patients in chronic forms of the disease may lead to acute pancreatitis, and they recommend treatment by splanchnicectomy.

NEUROGENIC CONTROL OF THE URINARY TRACT

a. Kidney

Transplantation of the kidney, successfully performed by Carrel and Guthrie (1906), proved that the totally denervated kidney can carry on all functions which are essential to life. The earliest studies on renal denervation, notably those of Quinby (1916) and Marshall and Kolls (1919), indicated a temporary increase in urinary secretion. Nearly all investigators have agreed that denervation causes no change in the elimination of phenolsulfonephthalein, sodium chloride, lactose, urea, and many other substances. The carefully controlled experiments of Rhoads, Van Slyke, Hiller, and Alving (1934) on dogs showed no consistent effect on either the excretory efficiency of the kidney or on the renal blood flow. These results in animals have been confirmed in man by Page and Heuer (1935*A* and *B*). Measurements of urea clearance and volume of urine secreted from the normal and the denervated kidney (resection of nerve fibers in the renal pedicle) failed to show any significant difference over a period of months following operation.

The possibility that the beneficial effect of sympathectomy and splanch-

abolished this response. More recent experiences (Kuntz, 1945) indicate that the sympathetic secretory fibers to the liver run in the fifth and sixth white communicant rami. Long (1940) has summarized the evidence in favor of a central nervous regulation of carbohydrate metabolism by the liver and pancreas. He cites the experimental work of Zunz and LaBarre (1928), which, although unconfirmed, lends basis to a rather attractive hypothesis of blood glucose regulation by the autonomic nervous system. This postulates that the level of the blood glucose passing through the sensitive hypothalamic centers determines the activity of the glands concerned with carbohydrate metabolism. Thus, when the hypothalamic glucose level is elevated, insulin secretion is stimulated through the vagi. On the other hand, when the level falls, glucose is liberated from the liver by the combined activity of the adrenal medulla and hepatic nerves. No criticism can be found of the view that sympathetic impulses can elevate the blood sugar level, but the relation of the vagi to insulin secretion is, in Long's opinion, more questionable. Until more convincing facts are established, it would seem that the major control of carbohydrate metabolism is to be found in the activity of the anterior pituitary, adrenal cortex, and islets of Langerhans. It is still quite possible that their activity is regulated directly by the composition of the blood passing through them.

There is also a certain amount of evidence that protein metabolism is mediated by autonomic impulses from the diencephalon. Freund and Grafe (1912) showed experimentally that it is augmented by the sympathetic and inhibited by the parasympathetic nerves. The secretion of bile, on the other hand, is stimulated, though only partially, by the vagus (Eiger, 1915).* The observations of Bainbridge and Dale (1905) show that the musculature of the biliary system responds in general to vagus and splanchnic stimuli much as does the musculature of the gastrointestinal tract.

More recent studies on the influence of neurogenic control of filling and emptying of the gall bladder and biliary tree are available from the work of Mallet-Guy and Guillet (1943 and 1944) and the more extensive discussion by Poilleux and Guillet (1947) before the French Surgical Congress. The observations of these surgeons from Lyons in the dog and man show that the splanchnic system inhibits the tone of the gall bladder and biliary tree. On the other hand, an increase in vagal activity leads to emptying of the gall bladder, an elevation of pressure within the biliary ducts, and relaxation of the sphincter of Oddi.

* Hillyard (1930) showed that the most important stimulus to the secretion of bile is a chemical one.

They may also exert a slight influence on the internal sphincter. This has been maintained by Learmonth (1931*A*) but denied by Denny-Brown and Robertson (1933). Resection of the superior hypogastric plexus produces no alteration in the cystometrogram (see p. 389, Chap. XIV).

NEUROGENIC CONTROL OF THE SEX ORGANS

While the development and functional activity of the sex organs are largely under the control of the endocrine glands (anterior pituitary and adrenal cortex), their reflex adjustment to environmental changes is regulated by the autonomic nervous system. In a general way the behavior of these opposed nerves follows the rules of homeostasis in other parts of the body. In states of well-being and contentment the parasympathetic holds the upper hand, and under these circumstances the pelvic viscera receive a maximal flow of blood and are easily stimulated. Under conditions of fear and worry the blood is shunted to the striated muscles, and with it irritability of the genital tract and sexual desire are temporarily lost.

a. The Male Sex Organs

Kuntz (1919) has shown that in the testicle unmyelinated nerve fibers follow the distribution of the vessels and do not invade areas of secretory tissue or tubules except as they accompany the arteries and veins. This is presumptive evidence that the spermatic plexus governs spermatogenesis only by its control of blood flow to the testicle.

In the control of the complex processes that lead up to orgasm and ejaculation, the involuntary nerves play the double role of engorging the penis with blood and causing ejaculation by contracting the smooth muscle of the vasa deferentia, seminal vesicles, and prostate. Eckhard (1863) found that stimulation of the sacral nerves in the dog causes erection of the penis. When the nervi erigentes are cut, the vessels in the penis contract (Nikolsky, 1879). Langley and Anderson (1895) stimulated the lumbar sympathetic rami (second, third, and fourth) and demonstrated vasoconstriction of the penile vessels. These investigators also confirmed the previous observation of Budge (1858), that stimulation of the sympathetic nerves causes contraction of the entire musculature of the ductus deferens and seminal vesicles. In addition, it has been shown by Simeone (1933) that when these fibers are paralyzed in the guinea pig, the transport of spermatozoa through the ductus epididymidis is delayed significantly and probably enough to render them devoid of fertilizing capacity. Learmonth (1931*A*) was able to show the discharge of seminal fluid in man on stimulation of the superior hypogastric plexus. After removal of the plexus

nicectomy in hypertension may be related to improved renal circulation has led to renewed investigation. This problem has been explored by Homer Smith, whose findings are reviewed in Chapter XII. From his observations it is apparent that renal circulation is controlled by both neurogenic and humoral mechanisms. Although the former may intermittently reduce renal blood flow and secretion in response to pain and other stimuli such as the assumption of the upright posture, the basal rate of urinary secretion is not influenced by splanchnic denervation. It is primarily under the control of the posterior pituitary hormone, which is regulated from the anterior hypothalamus by the supraopticohypothalamic tract (G. W. Harris, 1947; Pickford, 1947). In addition to this mechanism the neurogenic control of the recently discovered "renal shunt" via the splanchnic nerves of Trueta *et al.* (1946 and 1947) may be an additional important factor in emotional and traumatic anuria. Cort (1949) has proved that this renal shunt can be activated in the spinal animal through stimulation of any large sensory nerve and also from higher control stations—the vasomotor center in the medulla, the posterior hypothalamic nuclei, and areas 6 and 13 of the cerebral cortex.

Recent evidence of Wolf and Wolff (1951) indicates that, although splanchnicectomy does not increase basal renal blood flow, it does prevent or favorably modify reflexly induced renal vasoconstriction. As a consequence renal blood flow may be increased because downward fluctuations are lessened or abolished.

b. Ureter

The ureteral nerves are known to carry afferent impulses, but they subserve no definitely proven motor function Experimental stimulation, as well as the administration of adrenaline (Elliott, 1907), has failed to show any changes in ureteral caliber or peristalsis Kuntz (1945), however, states that these nerves may be concerned in the maintenance of ureteral tone and in reflex co-ordination of peristalsis in relation to contractions of the bladder.

c. Bladder

Physiological studies in man have proved that both the storage of urine in the bladder and its evacuation are mediated exclusively by the sacral parasympathetic nerves (Denny-Brown and Robertson, 1933; Evans, 1936; Langworthy, 1940).* The sympathetic fibers regulate the flow of blood.

* The sacral segments also give off the pudendal nerve to the external sphincter of the bladder. This has been regarded as a voluntary nerve, but the work of these investigators has shown that its tone is inhibited and that it opens only during the integrated act of micturition. It can only be closed voluntarily

observed in man after lumbodorsal sympathectomy (Newell and Smithwick, 1947).

In concluding this chapter on the nervous control of homeostasis, one should pause to consider to what extent the autonomic system functions in an independent manner. The concept of its purely automatic activity, although long since disproved, tends to recur in current articles and in our thoughts. Even Langley (1921), who proposed the term "autonomic" in 1898, felt that it suggested "a much greater degree of independence of the central nervous system than in fact exists." In the years since his book was written a mass of evidence has accumulated which indicates that there is a constant co-ordination of visceral and somatic activity. In the central nervous system it is not always possible to separate autonomic from cerebrospinal pathways. In the cortex, as shown in the beginning of this chapter, recent evidence has brought out the fact that there is a certain degree of autonomic representation. In the cerebellum, always considered the domain of somatic function alone, Moruzzi (1940) and Connor (1941) have discovered evidence for autonomic control over the medullary centers of respiration and circulation by the paleocerebellar cortex. On the other hand, representation of somatic activity in such a purely autonomic area as the hypothalamus has recently been pointed out by Hinsey (1940). Sheehan (1941) has summarized the interrelationship of the cerebrospinal and the vegetative systems by the statement that "one is left with a concept of a single nervous system physiologically speaking, where visceral and somatic activities are closely integrated, and where each is probably under a certain control of the other."

or injury to the first and second lumbar ganglia the power of ejaculation may be lost,* although this operation does not ordinarily impair the power of erection nor the sensation of orgasm. Munro and associates (1948) have studied potency and ejaculation in soldiers after transecting injuries of the spinal cord. Sense of orgasm is lost, but, barring injuries to the cord between T6 and L3 sufficient to destroy the sympathetic outflow that controls ejaculation or the destruction of the sacral cord and cauda equina, these patients are often able to have erection and to ejaculate viable spermatozoa in response to local stimulation.

b. The Female Sex Organs

In a general way the nervous control of the female genitalia is similar to that in the male. Kuntz (1945) has shown that, although the ovary is abundantly supplied with nerve fibers, their distribution is limited to the blood vessels and the fibromuscular tissue in the stroma. As in the male, sympathetic stimulation causes contraction of the smooth musculature of the tubular and glandular portions of the genital tract and constriction of the blood vessels. During sexual excitement the nervi erigentes cause engorgement of the clitoris and labia minora, a reaction comparable to erection in the male. This response is caused by a summation of psychic stimuli and afferent impulses conveyed from the external genitalia to the sacral cord by the pudendal nerve. At the moment of orgasm the reflex center in the lumbar cord emits an outburst of sympathetic stimuli, causing contractions of the Fallopian tubes, uterus, and Bartholin's glands.

Section of the extrinsic nerves to the female sex organs does not interfere with normal menstruation or reproduction. As far back as 1882, G. Rein reported birth of young in rabbits following section of all the extrinsic nerves to the uterus. Cannon *et al.* (1929) have observed normal parturition in their totally sympathectomized cats, and Fontaine and Herrmann (1932) have recorded cases of normal childbirth after resection of the superior hypogastric plexus. According to Gerstmann (1926), this can take place in women even after complete transection of the spinal cord. In the cat, Simeone and Ross (1938) observed an increased incidence of abortion in animals that became pregnant shortly after sympathetic denervation of the internal genitalia. The incidence of stillbirths was high in cats that became pregnant long after sympathectomy. Among the 10 cats that were studied, 1 had rupture of the uterus and failure of development of the abdominal breasts. None of these complications of pregnancy has been

* We are obtaining increasing clinical evidence that males may not necessarily be sterile or have any permanent loss of sexual function after bilateral excision of the first or even the upper three lumbar ganglia, and, if lost, the power of ejaculation may be regained after a number of months or years (see p 399)

upon the heart and blood pressure. A similar substance was liberated into the blood stream of both anesthetized and unanesthetized animals when generalized activity of the sympathetic nervous system was induced with the adrenal medulla excluded (Cannon and Britton, 1927; Newton, Zwemer, and Cannon, 1931). The substance was called "sympathin" by Cannon and Bacq in 1931. Sympathin was thought to be a compound of adrenine, or an adrenine-like substance, with a second chemical agent within the effector cell. There were thus two types of sympathin: "sympathin E" released from smooth muscle cells which contract upon nerve stimulation and "sympathin I" from those which respond to nerve stimulation by relaxation (Cannon and Rosenblueth, 1933). While sympathin I has not been demonstrated in action alone or isolated as a substance, noradrenaline, which differs from adrenaline in that it lacks a methyl group, has been found to have properties similar to those of sympathin E. It was suggested recently by von Euler (1946) that there are two types of excitor sympathin, one of which is adrenaline and the other is noradrenaline. He suggested the term sympathin N for noradrenaline. It is present in extracts of the adrenal medulla and in preparations of adrenaline (Goldenberg, Faber, Alston, and Chargaff, 1949).

Acetylcholine is thought to be the chemical agent by which the nerve impulse is transmitted from preganglionic to postganglionic neurones in ganglia and from postganglionic neurones to effectors in cholinergic neuroeffector systems (Dale, Feldberg, and Vogt, 1936; Kibjakow, 1933; Feldberg and Gaddum, 1934; Feldberg and Vartiainen, 1934; Feldberg, Minz, and Tsudzimura, 1934).

The sympathetic division of the autonomic nervous system is characterized by an action which is diffuse and sustained (Cannon, 1932). The liberation of adrenine and of sympathin as the result of activity in this division of the autonomic nervous system facilitates the diffuse action. On the other hand, activity of the parasympathetic division is characterized by sharp localization and short duration of activity. The remarkable speed with which acetylcholine is destroyed in the body by cholinesterase facilitates this type of action (cf. Rosenblueth and Simeone, 1934).

The history of the development of the concept of chemical mediation of the nerve impulse has been admirably described by Cannon (1934 and 1939*A*). The theory fits the observations well and offers an explanation for the fact that even when denervated, structures may respond to sympathetic activity elsewhere in the body as they did when innervated. As Cannon and Rosenblueth (1937) put it, ". . . it is clear that locally produced sympathin, circulating sympathin and circulating adrenine all

CHAPTER V

Pharmacology of the Autonomic Nervous System

Many of the fundamental concepts regarding the organization and function of the autonomic nervous system have been derived from studies of the actions of drugs and hormones upon the system itself and upon the structures innervated by it. For a detailed review and discussion of these observations, the reader is referred to the monograph of Cannon and Rosenblueth on *Autonomic Neuro-effector Systems* (1937). Recent studies on the interrelationships between various drugs and hormones and the autonomic nervous system have led not only to a better understanding of the physiology of the autonomic nervous system, but also to the development of useful drugs which mimic or potentiate the actions of this system, and to the development of some drugs which block the effects of its excitation.

I. Chemical Mediation of Nerve Impulses

Elliott (1904 and 1905) first pointed out the similarity between the responses of effectors to sympathetic nerve stimulation and to adrenaline injected after the nerve supply had been divided and allowed to degenerate. Five years later Dixon and Hamill (1909) observed that the responses of the heart to vagal stimulation and to the injection of muscarine were practically identical. The similarity between the effects of acetylcholine injections and of parasympathetic nerve stimulation was described by Dale (1914) and by Dale and Ewins (1914). The now classical experiment of Loewi (1921) demonstrated that vagal stimulation of the isolated frog heart released a substance which caused slowing of a second heart connected to the first through Ringer's solution. Stimulation of the cardiac accelerator nerves released a substance into the solution which caused acceleration of the second heart.

The first demonstration that a chemical agent is released into circulating blood when the hepatic or splanchnic nerves are stimulated in the absence of the adrenal glands is that of Cannon and Uridil (1921). The hormone mimicked the action of adrenaline and of sympathetic nerve stimulation

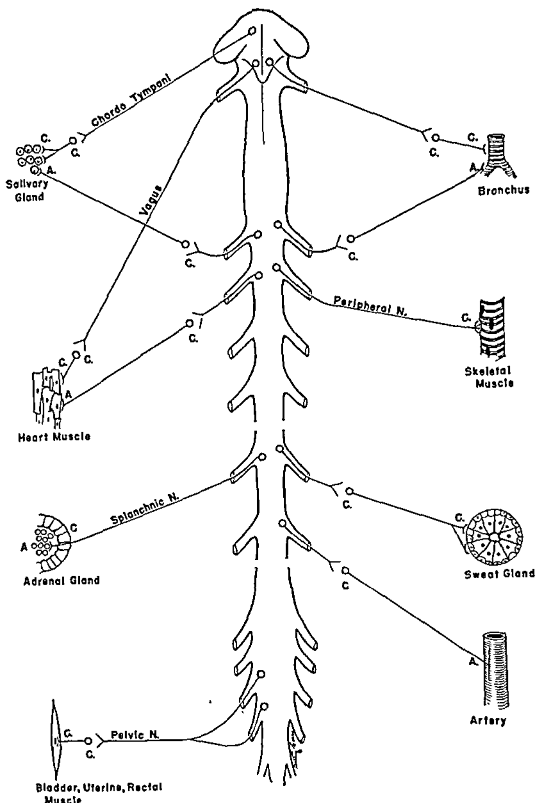


Fig. 23. Distribution of adrenergic and cholinergic fibers.

A Adrenergic nerve ending

C. Cholinergic nerve ending

(Redrawn and modified from Dale, H. H. "Nomenclature of fibres in the autonomic system and their effects." *J. Physiol*, 1934, 80: 10P–11P, courtesy of Cambridge University Press, Cambridge, England.)

work together to unify and synchronize the operations of the sympathetic system." Chemical mediation explains the activation of the many smooth muscle cells which normally are not innervated directly (Stöhr, 1928) and, at least in part, the recovery of tone by chronically denervated smooth muscle.

II. Drugs and Hormones Which Mimic Activity of the Autonomic Nervous System

It was recognized early that while adrenaline mimics most of the responses obtained when sympathetic nerves are stimulated, it does not reproduce all of them. The sudomotor effect of sympathetic stimulation, for instance, is mimicked in most animals * by acetylcholine and not by adrenaline In 1934 Dale suggested that, for functional purposes, the autonomic nervous system be grouped into two main subdivisions—"adrenergic" and "cholinergic" Preganglionic fibers in sympathetic ganglia, as far as is known, are all cholinergic. Within the parasympathetic nervous system fibers other than cholinergic have not been demonstrated. Vagal stimulation, after atropinization, does result in cardioacceleration (Jourdan and Nowak, 1934 and 1936), and this could represent an adrenergic effect within the parasympathetic nervous system. The nerve fibers responsible for this effect, however, are probably sympathetic nerve fibers which have joined the vagus fortuitously. Figure 23 shows diagrammatically the distribution of adrenergic and cholinergic fibers within the autonomic nervous system. Substances which mimic the adrenergic effects of nerve stimulation are referred to as "sympathomimetic," and those which mimic the action of cholinergic or parasympathetic nerves are known as "parasympathomimetic."

A. SYMPATHOMIMETIC AGENTS

Extracts of the adrenal medulla were shown, as early as 1895, by Oliver and Schäfer, to have pressor activity. The active principle in the saline extracts was isolated by Abel and Crawford in 1897 and was named epinephrine.† A glance at the structural formulae of epinephrine and of other sympathomimetic substances reveals their close relationship

* Haimovici (1948) has presented evidence that, in man, sudomotor activity is not entirely cholinergic but is in part adrenergic.

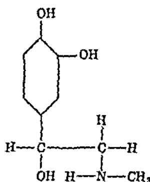
† Cannon preferred to call the substance liberated by the adrenal medulla into the circulation "adrenine" "Adrenalin" is the trade name given the hormone by its manufacturers, Parke, Davis & Company. As a general principle, the name of a chemical agent ends in "e" when its chemical formula is known When a preparation of the hormone was injected into an animal, Cannon referred to it as "adrenaline."

of adrenaline and can be taken orally as well as parenterally. The effective parenteral dose is five to ten times that of adrenaline, but the drug is less susceptible than adrenaline to oxidation within the body, and consequently the responses are longer lasting. Neo-synephrine lacks some of the cardioaccelerator action of adrenaline and the central nervous system stimulant action of ephedrine.

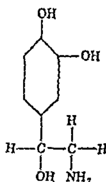
Noradrenaline (Arterenol). This hormone differs from adrenaline only in that it lacks one methyl radical from the aliphatic amino group. It has been found in the adrenal medulla in large amounts, in pheochromocytomas, and in preparations of adrenaline (Holton, 1949*A* and *B*; Goldenberg, Faber, Alston, and Chargaff, 1949). In contrast to adrenaline, which produces a largely systolic hypertension in man primarily by increasing the *cardiac output, noradrenaline causes a hypertension which is both systolic* and diastolic primarily by increasing the peripheral resistance (Goldenberg, Aranow, Smith, and Faber, 1950). From observations on the hemodynamic effects of noradrenaline in man, Goldenberg, Apgar, Deterling, and Pines (1949) have suggested that it may prove to be a useful agent for treating acute hypotensive states.

Ephedrine. Ephedrine is an alkaloid first isolated by Nagai in 1887 from Ma Juang, an herb used by the Chinese for over five thousand years (Weiss, 1932). It is chemically similar to adrenaline, differing from it in that it lacks the hydroxyl groups on the benzene ring and has an aliphatic chain longer than that of adrenaline by one carbon. The drug has the pressor actions of adrenaline but not the depressor. Ergotoxine, therefore, does not reverse its pressor effects. It is not destroyed readily in the body, and its action is longer lasting than that of adrenaline. Ephedrine may be taken orally in dosages of 15 to 45 mg every three or four hours. The parenteral dose is the same as the oral dose. It potentiates the action of adrenaline and of sympathetic nerve stimulation (Gaddum and Kwiatkowski, 1938). Its actions appear not to be potentiated by cocaine and by denervation, as are those of adrenaline.

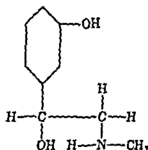
Benzedrine. This drug (racemic amphetamine sulfate) is closely related to both adrenaline and ephedrine and has many of the pharmacologic properties of both. It is even more resistant than ephedrine to destruction, and its action therefore is longer lasting than that of adrenaline or ephedrine. Benzedrine has the pressor actions of adrenaline and ephedrine, but its most striking characteristic is a strong stimulating action upon the central nervous system. Serota (1939) suggested that this stimulant action may be related to the drug's ability to increase the metabolism of the hypothalamus. Dexedrine (manufactured by Smith, Kline and



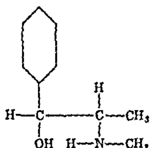
ADRENALINE



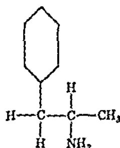
NORADRENALINE



NEO-SYNEPHRINE



EPHEDRINE



BENZEDRINE

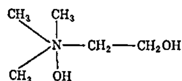
Adrenaline. This hormone is very potent and produces effects in minute amounts, an effective dose in man being 0.5 mg when injected subcutaneously. It is not effective when taken orally, but when injected parenterally it reproduces all the effects of widespread sympathetic activity, excepting the cholinergic ones Adrenaline mimics not only the contractile effects of nerve stimulation upon smooth muscle but the relaxing effects as well. In minute doses, only its relaxing effects are apparent, so that there is vasodilatation in the skin instead of the vascoconstriction resulting from larger doses. A slight drop in blood pressure, instead of a rise, is then observed. These "negative" effects of adrenaline are demonstrable by the introduction of drugs which block the "positive" or pressor (contractile) effects of the hormone. The best known of these agents are ergotoxine (Dale, 1906), dihydrogenated ergotoxine alkaloids (Rothlin, 1947), dibenamine (Nickerson and Goodman, 1947), and Priscoline (Chess and Yonkman, 1946). Adrenaline is rapidly destroyed when injected into the circulation. An amine oxidase (Philpot, 1940) was thought to play an important role in its destruction, but doubt has been cast upon this view recently (Bacq, 1949).

Neo-synephrine. This synthetic drug differs from adrenaline in lacking the hydroxyl group in the para position. It possesses most of the actions

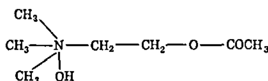
depressive states (Myerson, 1936), and for reducing the depth of anesthesia and narcosis (Myerson *et al.*, 1939; Michelsen and Verlot, 1939). Benzedrine and Dexedrine, by their further action upon the central nervous system, stimulate mental activity and reduce hunger. These drugs have been used for facilitating weight loss and ill-advisedly for counteracting mental fatigue.

B. PARASYMPATHOMIMETIC AGENTS

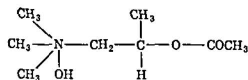
The drugs and hormones described above which mimic excitation of adrenergic sympathetic fibers belong to a group of phenyl aliphatic amines. Those which mimic activity of cholinergic autonomic nerve fibers are derivatives of choline or related to it, with the exception of the two classical parasympathomimetic drugs, pilocarpine and arecoline. Muscarine is not a choline ester, but its close similarity to the choline derivatives of this group is obvious upon inspection of its formula.



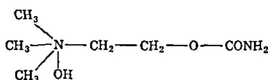
CHOLINE



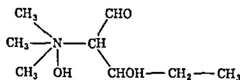
ACETYLCHOLINE



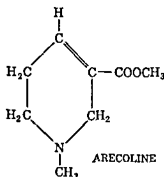
ACETYL-BETA-METHYLCHOLINE



CARBAMINOYLCHOLINE



MUSCARINE



ARECOLINE

Acetylcholine, or at least a compound indistinguishable from it, has been identified as the substance liberated at cholinergic nerve endings in the heart, in skeletal muscles, in autonomic ganglia, at certain vasodilator nerve endings, and within the central nervous system. It appears to be the agent

French) is the dextrorotatory, more active form of amphetamine sulfate. Benzedrine and Dexedrine are taken orally in doses of 5 to 10 mg.

Clinical Applications. The clinical usefulness of the sympathomimetic drugs lies, for the most part, in their ability to affect smooth muscle. Adrenaline remains unsurpassed in its dilator effects upon the bronchial smooth muscles. It is the drug of choice for symptomatic treatment in asthma. It is not entirely clear if the action of adrenaline in asthma is purely one of relaxation of the bronchiolar musculature or if, added to this, there is shrinkage of the mucous membrane lining the bronchial tree. Adrenaline is also as effective in other allergic manifestations such as hives and angioneurotic edema. Adrenaline, however, is readily destroyed within the body and its action is short lasting. When injected intravenously, its effect is over in three to five minutes. Subcutaneously, it acts somewhat longer. *Preparations of adrenaline in oil are designed to permit slower* absorption and longer action. The action of adrenaline upon the bronchioles is so effective that therapy can be achieved with such small doses that the gastrointestinal and cardiovascular systems are affected very little if at all.

All of the sympathomimetic agents have been found useful for raising the blood pressure, particularly when hypotension is on a neurogenic basis, i.e., after spinal anesthesia. Ephedrine has been found the most useful in this regard because of its prolonged action. Recently, Goldenberg, Apgar, Deterling, and Pines (1949) have suggested that noradrenaline, which has the excitor and not the inhibitor properties of adrenaline, may be a useful drug in various types of acute hypotension, including that due to hemorrhage. This, however, must await further evidence for judgment, since it is not in keeping with some of the accepted principles in the management of traumatic shock. Noradrenaline and Neo-synephrine are the drugs of choice for counteracting the hypotension which occurs immediately after completion of sympathectomy for hypertension.

The sympathomimetic agents, especially adrenaline, Neo-synephrine, and ephedrine, have found extensive application as topical agents to produce local vasoconstriction and detumescence of mucous membranes. Neo-synephrine and ephedrine have been found preferable for this purpose because they lack the dilator component of adrenaline, and there is less postshrinkage swelling

Ephedrine has been found to counteract some of the muscle weakness in myasthenia gravis, but it is not nearly so effective as Prostigmine in this disease. Ephedrine has some stimulant action upon the central nervous system, but it is surpassed by amphetamine. The latter has been used for treating narcolepsy (Prinzmetal and Bloomberg, 1935) and mental

to produce any effects at all (Weiss and Ellis, 1934), and even larger doses are ineffective when injected subcutaneously or intramuscularly (Carmichael and Fraser, 1933). Orally, acetylcholine produces effects only exceptionally (Kovacs *et al.*, 1936), and then only when given in enormous doses (2 gm). Patients with myasthenia gravis have shown some improvement in muscle power after subcutaneous injections of acetylcholine (Fraser *et al.*, 1937). When present in excessive concentrations, acetylcholine inhibits its own activity by blocking the responses of postganglionic neurons (G. L. Brown and Feldberg, 1936) and of striated muscle (Rosenblueth and Morison, 1937). Acetylcholine has been of inestimable value for the elucidation of physiological problems in the laboratory. Clinically, however, it has not been useful because of its extraordinary instability. Recently, Oudot (1947) reported his laboratory and clinical experiences with intra-arterial injections of acetylcholine. He did not find it as effective an agent for producing local vasodilatation in man as in the experimental animal, but he considered the drug in 200-mg doses as of possible use in the sequelae of cold injury and in occlusive peripheral vascular disease.

Acetyl-beta-methylcholine (Mecholyl). The introduction of a methyl group into acetylcholine in the beta position converts it into a compound which, while retaining most of the actions of acetylcholine, is far more stable and therefore more effective as a therapeutic agent. Acetyl-beta-methylcholine (Mecholyl) is two hundred times as active as acetylcholine when injected intravenously (Weiss and Ellis, 1934). The drug is effective when administered by mouth in doses of 100 mg every three or four hours. Larger doses are needed orally than when injected subcutaneously, but there are fewer untoward reactions. In paroxysmal tachycardia, for example, the subcutaneous administration of 20 to 30 mg has been found effective. Atropine in doses of 0.5 to 1.0 mg is the antidote for untoward reactions to the drug. Acetyl-beta-methylcholine lacks the nicotinic action of acetylcholine on autonomic ganglia, but possesses it in the case of striated muscle. It has been found effective in myasthenia gravis. It should not be administered intravenously.

Carbaminoylcholine (Doryl). This synthetic ester of choline has all the actions of acetylcholine and differs from it principally in that it is not readily susceptible to destruction by cholinesterase and therefore possesses a prolonged period of action. For the same reason, however, its actions are not potentiated by substances which inhibit the activity of cholinesterase (physostigmine and Prostigmine).

Carbaminoylcholine has a rather selective parasympathomimetic action upon the gastrointestinal and urinary tracts. These organs are influenced

the transmission of the nerve impulse at synaptic stations in the central and autonomic nervous systems, and at certain neuroeffector junctions. Its actions resemble those of excitation of the craniosacral division of the autonomic nervous system and are representative of this group of drugs and hormones.

In general, the parasympathomimetic drugs have two groups of actions —the nicotine-like and the muscarine-like. The former consist of excitation of postganglionic autonomic neurons, of skeletal muscle cells, and of the adrenal medulla. These actions are not blocked by atropine, but curare in large doses inhibits them or blocks them completely. The muscarine-like effects are those upon the heart, smooth muscle, and glands, especially the salivary, sweat, and lacrimal glands. They are readily blocked by atropine. In fact, the nicotinic actions of acetylcholine are not ordinarily discernible without first blocking its muscarine effects with atropine. In describing certain actions of the parasympathomimetic drugs as nicotine-like, it is important to note that the reference is made here to the excitatory effects of nicotine and not to its paralyzant effects upon autonomic ganglia for which nicotine is more commonly known. The excitatory action of nicotine on autonomic ganglia, for instance, was clearly recognized by Langley and Dickinson in 1889. The brief application of a warm solution of 0.1 per cent nicotine locally to the superior cervical ganglion produced changes in the eye and in the blood vessels of the ear comparable to the effects of electric stimulation of the ganglion (Langley, 1901*A*). This effect could be produced repeatedly if the drug was washed off the ganglion with salt solution. Prolonged application, however, or the use of stronger solutions produced a block to the effects of preganglionic stimulation of the cervical sympathetic, while stimulation of the postganglionic fibers produced its usual effects. The block, therefore, was at the ganglion, and presumably at the synapse between pre- and postganglionic neurons. This property of nicotine to stimulate in small concentrations and to block in greater concentrations is not unique. Acetylcholine, for example, while predominantly excitatory at the ganglion, will block transmission in high concentration.

Acetylcholine. Acetylcholine is a very unstable ester and in the body is destroyed by cholinesterase with almost unbelievable rapidity. The esterase is found in innervated effectors and especially in the proximity of nerve endings. This organization and degree of activity are essential to the theory of chemical mediation by acetylcholine in such speedily acting tissue as striated muscle. So easily is acetylcholine destroyed by body fluids in man that large doses intravenously (about 60 mg per minute) are necessary

the nicotine-like actions of acetylcholine upon autonomic ganglia. Its parasympathomimetic action has found no clinical application.

Clinical Applications. While the parasympathomimetic drugs are among the most active agents known, they have been used relatively little in the clinic. The demonstrable effects of acetylcholine, when administered in large doses intravenously or subcutaneously, are of academic interest only. When injected subcutaneously or intravenously, the substance is destroyed too rapidly by cholinesterase to be effective clinically unless protected from cholinesterase by physostigmine or Prostigmine. When injected intra-arterially, however, it causes an intense local vasodilatation, and this may be useful especially in acute vascular insufficiency (Oudot, 1947). Mecholyl (acetyl-beta-methylcholine) is longer acting and has been used clinically. In diseases of the peripheral circulation, the doses required for vasodilatation are so large that the side effects from the drugs make them impractical. An ingenious method for carrying acetylcholine directly to the blood vessels, iontophoresis, was advocated by Duryee and Wright (1937). The drug was introduced into the skin by means of a galvanic current of 20 ma. Little has come of this method during the past decade, and it is seldom used in the treatment of peripheral vascular disease. The fact that Mecholyl has been shown to be helpful in myasthenia gravis is of little clinical importance, since Prostigmine is much more effective and easy to use.

Mecholyl has been found useful in the treatment of paroxysmal tachycardia. For this purpose the drug may be injected subcutaneously in doses of 20 to 30 mg. While it is effective, untoward reactions do occur, including nausea, vomiting, sweating, and asthma. Hypotension and heart block may occur. These reactions, muscarinic effects, are controlled by atropine, which should always be at hand when Mecholyl is used.

Pilocarpine has been widely used as an agent for stimulating and testing sweat gland activity. We have not used it for this purpose in man, however, because of the undesirable side effects of the drug related to its muscarine-like action.

III. Cholinesterase Inhibitors

The rapid destruction of acetylcholine at ganglionic synapses and at neuroeffector junctions is brought about by action of the enzyme cholinesterase. Substances which inhibit the activity of cholinesterase enhance the responses to stimulation of cholinergic sympathetic fibers and of the parasympathetic division of the autonomic nervous system. Likewise, they potentiate the effects of injections of the choline esters, especially those

by doses which have no appreciable effect upon the cardiovascular system. It has been used clinically to control postoperative urinary retention and the urinary stasis of the tabetic bladder. The oral and parenteral doses are approximately the same (0.3 to 0.6 mg two or three times a day). While both acetyl-beta-methylcholine and carbaminoylcholine have been used to induce vasodilatation in peripheral vascular disease, neither has proved to be clinically useful for this purpose.

The methane of beta-methylcholine (Urecholine) has supplanted carbaminoylcholine for clinical purposes because it lacks some of the undesirable nicotine-like effects of Doryl which were difficult to block with atropine (Starr and Ferguson, 1940). Urecholine, in dosages of 10 to 30 mg by mouth or up to 5 mg intramuscularly repeated two or three times a day, has been found useful for counteracting some of the undesirable gastrointestinal effects of vagectomy and for preventing and treating postoperative ileus and urinary retention (Machella *et al.*, 1947; Stein and Meyer, 1949).

Pilocarpine. This alkaloid prepared from the South American plants of the genus Pilocarpus mimics only the muscarinic actions of acetylcholine and of cholinergic nerve stimulation. The effects of the drug are readily blocked by atropine. It causes motor activity of the gastrointestinal tract, nausea, and vomiting. When injected parenterally in doses of 0.1 to 0.2 mg per kilogram of body weight, it excites the salivary glands and the sweat glands to secrete profusely, and the drug has been used as an agent for testing sweat gland activity. Pilocarpine may prove useful for distinguishing preganglionic denervation of sweat glands as opposed to denervation by postganglionic or peripheral neurectomy (Hyndman and Wolkin, 1941*B*; Simeone *et al.*, 1951). The miotic effects upon the eye have no advantage over similar effects of other drugs

Muscarine. Muscarine is the active alkaloid obtained from certain poisonous mushrooms, and the similarity between its effects upon the heart and the effects of vagal stimulation formed part of the foundation upon which was built the theory of the chemical mediation of nerve impulses. Other than this point of historical interest and the fact that it is the active alkaloid of a group of poisonous mushrooms, muscarine is of no clinical interest per se.

Arecoline. This alkaloid, obtained from areca nuts, is interesting in that it possesses the muscarinic actions of acetylcholine and of excitation of the craniosacral division of the autonomic nervous system without any chemical similarity with muscarine and acetylcholine. It does not possess

Other Cholinesterase Inhibitors. The convulsant and excitatory effects of the alkaloid strychnine have long been recognized and have been the subject of numerous studies. The mechanism of action has not been clearly understood but it may, like Prostigmine, be due to an inhibition of cholinesterase activity, particularly within the central nervous system. A number of compounds have been described recently which also inhibit the action of cholinesterase (diisopropyl fluorophosphate, hexaethyltetraphosphate, and tetraethylpyrophosphate). These drugs are of great theoretical interest (Dixon and Needham, 1946; Nachmansohn *et al.*, 1948). With the exception of tetraethylpyrophosphate, however, which may prove to be a useful adjunct in the treatment of myasthenia gravis (cf. Stone and Rider, 1949), they have not found clinical application. An excellent review of the pharmacology of drugs which inhibit cholinesterase activity has been written by Koelle and Gilman (1949).

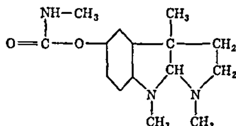
IV. Potentiation of Autonomic Responses

A. CHEMICAL AGENTS

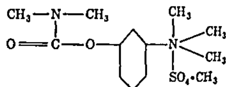
The potentiation of cholinergic effects by the administration of Prostigmine and physostigmine has already been described. These substances exert their effects by inhibiting the destruction of the chemical mediator, acetylcholine, at autonomic ganglia or in the periphery. The potentiation of adrenergic effects can be accomplished by a variety of drugs, but the mechanism of their actions is not so well understood as is that of Prostigmine and physostigmine.

Cocaine. The potentiating effect of this alkaloid was first reported in 1910 by Fröhlich and Loewi. The responses of both smooth muscle and glands to sympathetic nerve stimulation are increased after administration of the drug. It potentiates not only the positive actions of adrenaline but the negative as well (Rosenblueth, 1931). There appears to be some specificity to the sensitizing action of cocaine upon responses to adrenaline. The responses to ephedrine, for instance, are not potentiated. The mechanism of this potentiating action is not clear. It has been suggested that cocaine may cause an increase in permeability of the effector cell membranes, thereby permitting more mediator to enter the cells, or it may delay the destruction of the mediator after it has reached the cells (cf. Cannon and Rosenblueth, 1937). The latter theory is plausible because of the analogy with drugs which potentiate cholinergic activity. Cocaine inhibits the activity of amine oxidase (Philpot, 1940) and, if adrenaline is destroyed by amine oxidation, this would explain the potentiating action

of acetylcholine, which is very unstable and especially susceptible to destruction by cholinesterase. The most useful and best-known cholinesterase inhibitors are physostigmine (eserine) and Prostigmine (neostigmine).



PHYSOSTIGMINE (ESERINE)



PROSTIGMINE (NEOSTIGMINE) METHYLSULFATE

Physostigmine (Eserine). Physostigmine, also known as eserine, is an alkaloid prepared from the Calabar bean. Its structural relationship to Prostigmine is illustrated in the formulae above. The drug has been used for years by ophthalmologists as an ingredient of collyria for inducing miosis. Eserine does not act on denervated smooth muscle, and its effects are due to its inhibition of the destruction of the acetylcholine liberated at the myoneural junction by impulses normally reaching it. The drug is effective in relieving the muscle weakness of myasthenia gravis, but its side effects and short duration of activity make it less desirable than Prostigmine. When injected subcutaneously, the dosage is 0 5 to 1 0 mg; orally, the dose is twice this. Eserine decreases the activity of cholinesterase, and the spared acetylcholine may exert both muscarinic and nicotinic actions. The former are blocked by atropine, the latter by nicotine and curare.

Prostigmine (Neostigmine). This alkaloid is prepared synthetically and resembles physostigmine in both structure and function. Both experimentally and clinically, it has fewer undesirable side effects than eserine when administered systemically. It has been used in surgery for preventing and treating postoperative distention and urinary retention because it promotes the muscarinic action of parasympathetic nerve stimuli reaching the intestine and urinary bladder. The drug must not be given, however, if there is any suspicion that distention is due to mechanical obstruction (cf. Gordon, 1940). Prostigmine (neostigmine) is the drug of choice in the treatment of myasthenia gravis (Viets and Schwab, 1939; Viets, 1948; C. T. Stone and Rider, 1949). The bromide salt is used for oral administration; the methyl sulfate parenterally. The oral dose is 15 to 30 mg of the drug, repeated as needed. Parenterally, the initial dose is 0.5 mg subcutaneously. This may be increased as indicated up to 1.5 mg and may be repeated as needed. Atropine should be kept available as an antidote for untoward reactions.

Part of the evidence for supersensitivity following denervation is the paradoxical pupillary reaction of Anderson (1903) and Meltzer and Auer (1904). In animals (cat and rabbit), under conditions in which adrenine is secreted into the circulation, the chronically denervated miotic pupil, ordinarily smaller than the contralateral innervated pupil, becomes larger than the normal control, hence the "paradoxical" reaction. We have tested this in two patients who had long-standing sympathetic denervation of the eye. One had postganglionic denervation by excision of the superior cervical ganglion; the other had preganglionic denervation as the result of a Klumpke type of birth paralysis. The injection of adrenaline in one and ether anesthesia with careful observations during the phase of excitement in the other failed to produce a paradoxical pupillary reaction. It is possible that the dilator fibers of the pupil are less well developed or more strongly opposed by the constrictors in man than they are in lower animals.

On the basis that the supersensitivity of smooth muscle to circulating hormones after postganglionic denervation might account for recurrences of vasospasm during the early postoperative period after sympathectomy in Raynaud's disease (Freeman *et al.*, 1934; Smithwick *et al.*, 1934), Telford (1935) and Smithwick (1936) independently devised techniques for preganglionic denervation of the upper extremity. Increased sensitivity of blood vessels does occur after denervation in the dog (Essex *et al.*, 1943), the rabbit and monkey (White *et al.*, 1936), the monkey (Ascroft, 1937), and in man (Simeone and Felder, 1951). While this phenomenon could play a role in early recurrences and especially in patients in whom "local fault" (cf. Lewis, 1936) is prominent, it has been demonstrated by several observers that nerve regeneration has usually occurred in patients who show recurrence of vasospasm (Smithwick, 1936, 1940*A;* Simmons and Sheehan, 1939; Haxton, 1947; Barcroft and Hamilton, 1948*A* and *B*). In a recent study of patients on whom sympathectomy had been done for clinical vasospasm of the extremities, Felder *et al.* (1949) showed that recurrence of vasospasm was attended by demonstrable functional activity of both vasomotor and sudomotor nerves. It appears, then, that regeneration of sympathetic nerves or, less likely, the reorganization of neurons (Geohegan and Aidar, 1942) within the sympathetic nervous system is actually of first importance in the recurrence of vasospasm after sympathectomy. Kirgis *et al.* (1950) have recently arrived at the same conclusion from experiments in animals. The techniques for denervation of the extremities should be directed, therefore, toward effecting as complete a

of cocaine. Bacq (1949), however, states that the deamination of adrenaline by amine oxidase is unlikely. Further evidence, by analogy, that cocaine may act by preventing the rapid destrtuction of adrenaline is the demonstration by Bacq (1936*A*) that pyrogallol potentiates the action of adrenaline presumably by interfering with its destruction by oxidation.

The potentiating effect of cocaine upon the shrinking action of adrenaline on the mucous membranes has been employed clinically, but the risk of developing cocaine addiction after the use of such solutions is so great that they should not be used except under very special circumstances. Cocaine is used as a mydriatic in opthalmology. It acts here not directly upon the dilator fibers of the iris, but by potentiating the dilator effects of normal sympathetic impulses reaching the iris. It does not act on denervated smooth muscle.

B. DENERVATION

As a general principle, effectors which have been denervated yield greater responses when stimulated than they did before denervation. This phenomenon is demonstrable in experimental animals for all neuroeffector systems, both vegetative and somatic, investigated to date. Indeed, it has been demonstrated for sympathetic neurons themselves and for neurons within the central nervous system. The evidence has been assembled by Cannon (1939*B*) and described as "A Law of Denervation" which states that "when in a series of efferent neurones a unit is destroyed, an increased irritability to chemical agents develops in the isolated structure or structures, the effect being maximal in the part directly denervated." In addition to increased responsiveness to chemical agents, partially denervated structures (smooth muscle, ganglia, adrenal gland) show increased responsiveness to nerve impulses reaching them. The evidence for the Law of Denervation and its implications have been described recently (1949) by Cannon and Rosenblueth in their monograph, *The Supersensitivity of Denervated Structures. A Law of Denervation.* Hampel had demonstrated that postganglionic denervation led to greater sensitization than preganglionic denervation. Simeone (1937) confirmed these observations and demonstrated that the increased sensitivity to adrenaline of the denervated nictitating membrane disappears as the nerve supply regenerates. In keeping with these observations in the cat is the report of Simmons and Sheehan (1939) in which they demonstrated that by the time regeneration had occurred after sympathetic denervation of the upper extremity, the increased sensitivity of blood vessels to adrenaline had disappeared.

Part of the evidence for supersensitivity following denervation is the paradoxical pupillary reaction of Anderson (1903) and Meltzer and Auer (1904). In animals (cat and rabbit), under conditions in which adrenine is secreted into the circulation, the chronically denervated miotic pupil, ordinarily smaller than the contralateral innervated pupil, becomes larger than the normal control, hence the "paradoxical" reaction. We have tested this in two patients who had long-standing sympathetic denervation of the eye. One had postganglionic denervation by excision of the superior cervical ganglion; the other had preganglionic denervation as the result of a Klumpke type of birth paralysis. The injection of adrenaline in one and ether anesthesia with careful observations during the phase of excitement in the other failed to produce a paradoxical pupillary reaction. It is possible that the dilator fibers of the pupil are less well developed or more strongly opposed by the constrictors in man than they are in lower animals.

On the basis that the supersensitivity of smooth muscle to circulating hormones after postganglionic denervation might account for recurrences of vasospasm during the early postoperative period after sympathectomy in Raynaud's disease (Freeman *et al.*, 1934; Smithwick *et al.*, 1934), Telford (1935) and Smithwick (1936) independently devised techniques for preganglionic denervation of the upper extremity. Increased sensitivity of blood vessels does occur after denervation in the dog (Essex *et al.*, 1943), the rabbit and monkey (White *et al.*, 1936), the monkey (Ascroft, 1937), and in man (Simeone and Felder, 1951). While this phenomenon could play a role in early recurrences and especially in patients in whom "local fault" (cf. Lewis, 1936) is prominent, it has been demonstrated by several observers that nerve regeneration has usually occurred in patients who show recurrence of vasospasm (Smithwick, 1936, 1940*A;* Simmons and Sheehan, 1939; Haxton, 1947; Barcroft and Hamilton, 1948*A* and *B*). In a recent study of patients on whom sympathectomy had been done for clinical vasospasm of the extremities, Felder *et al.* (1949) showed that recurrence of vasospasm was attended by demonstrable functional activity of both vasomotor and sudomotor nerves. It appears, then, that regeneration of sympathetic nerves or, less likely, the reorganization of neurons (Geohegan and Aidar, 1942) within the sympathetic nervous system is actually of first importance in the recurrence of vasospasm after sympathectomy. Kirgis *et al.* (1950) have recently arrived at the same conclusion from experiments in animals. The techniques for denervation of the extremities should be directed, therefore, toward effecting as complete a

denervation as possible and toward the prevention of regeneration, with less concern for the possible development of supersensitivity following postganglionic denervation.

V. Drugs Which Block Autonomic Activity

A number of drugs have been developed which effectively block the transmission of the nerve impulse at interneuronal synapses as well as at the neuroeffector junction. Those acting upon sympathetic neuroeffector systems have been widely called "adrenolytic" or "sympatholytic" drugs. Morison and Lissak (1938) presented evidence that, in vitro, adrenaline is destroyed more rapidly in the presence of the benzodioxane 933F. With this exception, there is no evidence that the blocking agents commonly used destroy adrenaline or sympathin, and until more evidence is available they should be referred to as "blocking agents" (Nickerson and Goodman, 1947; Simeone and Sarnoff, 1947; Nickerson, 1949).

Autonomic blocking agents may be divided, for convenience, into two main classes: those which block the effects of activation of "adrenergic" nerve fibers (Dale, 1934) and those which block the effects of "cholinergic" nerve stimulation.

A. ADRENERGIC BLOCKING AGENTS

Ergot and Its Derivatives. In 1905 Dale and, independently, Sollman and Brown (1905) demonstrated that crude extracts of ergot nullified or reversed the pressor actions of adrenaline injected intravenously. The details of these effects were described by Dale in 1906, and, with the exception of the purification and the more recent modification of the ergot alkaloids (cf. Rothlin, 1947), little has been added to those early data. The modification of the vascular effects of adrenaline by ergotoxine provided some of the evidence for the existence of adrenergic vasodilator nerves in the sympathetic nervous system. Some of the arguments for the theory of the chemical mediation of the nerve impulse (Cannon and Rosenblueth, 1937) depend upon observations on the effect of ergotoxine on the actions of adrenaline and of sympathetic nerve stimulation.

The adrenergic blocking action of ergotoxine has not found clinical usefulness. More recently, the component ergotoxine alkaloids have been *modified by hydrogenation (Stoll and Hoffman, 1943). Dihydrogenation* made the ergotoxine alkaloids more effective blocking agents and decreased their direct contractile effect upon smooth muscle. A priori, these changes would be expected to make the drugs more useful in the treatment of such

disorders as hypertension and peripheral vascular disease (Goetz, 1949; Goetz and Katz, 1949). Freis *et al.* (1948) reported their experiences with the use of the three hydrogenated ergotoxine alkaloids (dihydroergocornine, dihydroergokryptine, and dihydroergocrystine) in the treatment of hypertension. Their results were variable. The drug was effective when given orally as well as when administered intravenously in doses of 0.5 mg. The effective oral dose, however, was ten to twenty times the intravenous dose. They reported a few untoward reactions, such as nasal stuffiness and nausea, vomiting, and postural hypotension. To date, the experience has not been large enough to warrant definite conclusions, and the authors suggested further trials in hypertensive patients who showed some hypotensive effects from the drugs.

Benzodioxanes. The best known of the benzodioxane derivatives synthesized by Fourneau is the piperidinomethyl compound, 933F. It blocks the action of adrenaline, of circulating sympathin, and, to a lesser extent, the positive effects of direct sympathetic nerve stimulation. The local application of 933F to a sympathetic ganglion can block the transmission of nerve impulses through it. Other benzodioxane compounds (such as 883F) can block the effects of direct sympathetic nerve stimulation more effectively than 933F. In the periphery, these compounds act directly upon the effector cells, but their mechanism of action is not understood.

The benzodioxanes have proved to be very important tools in the physiologic investigations of autonomic neuroeffector systems (cf. Cannon and Rosenblueth, 1937), but until recently they had no clinical application. In 1947 Goldenberg, Snyder, and Aranow advocated the use of piperidinomethylbenzodioxane (933F) as a diagnostic agent in hypertension caused by pheochromocytoma. When the drug is administered during sustained hypertension or during a paroxysm of hypertension, there is a prompt and significant drop in the blood pressure in most patients with pheochromocytoma, the whole reaction being over in about fifteen minutes or less (Kositchek and Rabwin, 1950). In the case of "essential" or other types of hypertension there is either no effect from the drug or a temporary further increase in pressure. This increase in pressure is occasionally alarming and makes unwarranted the use of this test for routine screening purposes in all hypertensives. The recommended dosage is 10 mg of the drug intravenously per square meter of surface area. Fatalities have not been reported after the use of this drug in pheochromocytoma, but there have been severe side effects (Drill, 1949; Prunty *et al.*, 1950). Though rare, false negative results do occur (Dana and Calkins, 1949; Prunty *et al.*,

1950; Goldenberg and Aranow, 1950). The general problems involved in the diagnosis and management of pheochromocytoma have been discussed by Smithwick *et al.* (1950) (see p. 339).

Recently, Goldenberg and Aranow (1950) summarized their own experience and that of others in 62 patients with proved pheochromocytoma. Fifty-nine of them showed a positive benzodioxane test. Three showed false negative tests, and these were attributed as possibly being due to the existence of a hypertension which outlasts the immediate presence or activity of the tumor. The test depends upon the ability of the drug to block the pressor effects of the circulating hormones liberated by the adrenal medullary tumors (adrenine, noradrenaline). Prunty *et al.* (1950) present data suggesting that the problem may not be as simple as this, and further investigation is needed. No significant response is obtained if the drug is injected in the absence of hypertension, whether sustained or paroxysmal.

Dibenamine. This drug, a war-gas derivative and representative of a group of beta-haloalkylamines possessing similar properties, has a very specific blocking effect against the positive actions of sympathetic nerve stimulation and adrenaline injection (Fig. 24). Like most other substances which block the effects of sympathetic excitation, it is more effective in blocking the actions of adrenaline and of circulating sympathin than those

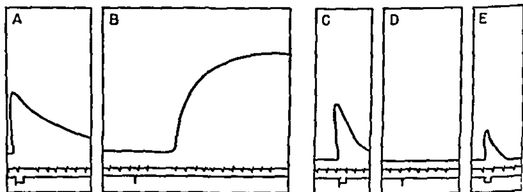
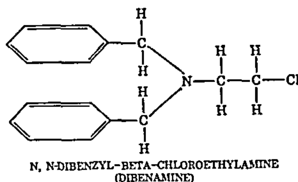


Fig. 24. Effect of dibenamine upon contractions of nictitating membrane in response to adrenaline and to electric stimulation of cervical sympathetic.

A. Response of unsensitized nictitating membrane to electric stimulation (five maximal shocks per second for five seconds). B. Response of same membrane to 1 cc of 1:25,000 adrenaline injected intravenously. Dibenamine, 40 mg per kilogram, injected in interval between B and C. C. Response of nictitating membrane to same stimulus as in A, five minutes after injection of dibenamine. D. Failure of nictitating membrane to respond to two and a half times the dose of adrenaline used in B, eight minutes after injection of dibenamine. E. Response of nictitating membrane to same electric stimulus as in A and C, twelve minutes after injection of dibenamine. Note that the effect of adrenaline is completely blocked, while that of nerve stimulation is only diminished. (Reproduced from Simeone, F. A., and Sarnoff, S. J. "The effect of dibenamine on autonomic stimulation." *Surgery,* 1947, **22:** 391–401, courtesy of C. V. Mosby Co., St. Louis.)

of direct sympathetic nerve stimulation (Simeone and Sarnoff, 1947). Dibenamine does not exert its effects immediately upon injection but requires half an hour or more before its effects are maximal (Fig. 25). It has the advantage, however, of being effective for long periods of time, so that injections of even small doses are not necessary more frequently than once or twice a day. This is in contrast to the shorter duration of action of the benzodioxanes. The drug should be used only intravenously and should be injected very slowly in dosages of 5 mg per kilogram of body weight. The full amount is administered during one and a half to three hours.



N, N-DIBENZYL-BETA-CHLOROETHYLAMINE
(DIBENAMINE)

THE TIME FACTOR IN THE ACTION OF DIBENAMINE

RESPONSE OF NICTITATING MEMBRANE (CENTIMETERS × 10)

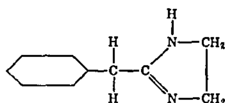
TIME (MINUTES)

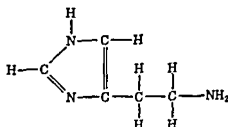
Fig. 25. Time factor in action of dibenamine in a typical experiment.

Broken line represents responses of nictitating membrane to electric stimulation (twenty maximal shocks per second for five seconds); solid line represents responses of nictitating membrane to adrenaline injected intravenously. Note that the blocking action is greater and develops more rapidly against adrenaline than against nerve stimulation. (Reproduced from Simeone, F. A., and Sarnoff, S. J. "The effect of dibenamine on autonomic stimulation." *Surgery*, 1947, 22: 391–401, courtesy of C. V. Mosby Co., St. Louis.)

When tested clinically, it has been reported as useful in diseases of the peripheral circulation (Console, 1948). A brief personal experience, however, indicated that the side effects, especially those upon the central nervous system, were too great to make this a safe drug for routine use (Simeone and Sarnoff, 1947). The drug has been used successfully in the diagnosis and treatment of pheochromocytoma (Spear and Griswold, 1948), in the treatment of hypertension (Wunsch *et al.*, 1950), and in acute glaucoma (Christensen *et al.*, 1948). While it is useful when administered with caution in acute conditions, its use over prolonged periods of time is probably ill advised. Its protective action against ventricular fibrillation (Nickerson and Goodman, 1947) has not had clinical trial.

Priscoline. This synthetic imidazoline is chemically related to histamine and to pilocarpine and has many of the actions of these two drugs. It causes


BENZYL-IMIDAZOLINE (PRISCOLINE)


HISTAMINE

certain smooth muscles to contract (pilomotors, nictitating membrane of the cat), excites gastric secretion, and has some other parasympathomimetic effects. In addition, however, Priscoline blocks the positive actions of adrenaline injected intravenously and to a lesser extent the effects of sympathetic nerve stimulation. It is interesting that, as in the case of dibenamine, the cardioaccelerator effects of stimulating the cardiac nerves and the mydriatic effects of stimulating the cervical sympathetic trunk in the cat are not blocked by Priscoline. There is evidence that the drug has a direct histamine-like action on the blood vessels in the periphery. Because of its adrenergic blocking properties and its direct vasodilator action, the drug has been recommended for improving the circulation in peripheral vascular disease and for eliminating the vasospasm attending poliomyelitis (Grimson, Reardon, *et al.*, 1948; E. Smith *et al.*, 1948; M. P. Rogers, 1949; Reilly and Barsanti, 1950). Eiben (1950) has used Priscoline early in patients with poliomyelitis who had demonstrable spasm in muscles of the back and thighs. He used doses of 25 to 50 mg orally or intramuscularly four times a day. There was no demonstrable relief of spasm, and only a few patients reported any relief of pain. In one patient the skin temperature of a blanched, cold, paralyzed extremity became normal after Priscoline. One patient had a severe reaction to the drug characterized by marked hyperten-

sion, pallor, cyanosis, and apprehension. The reaction experienced with Etamon Chloride had the same manifestations. Console *et al.* (1950) found Priscoline effective in controlling spontaneous and induced attacks of hypertension in a patient with pheochromocytoma. The drug can be taken orally in doses of 25 to 50 mg four to six times a day. It may be administered intravenously in doses of 50 to 100 mg.

Our personal experience with Priscoline in patients with Raynaud's disease, thromboangiitis obliterans, and in one patient who appeared to have an admixture of phasic vasospasm and erythromelalgia has been disappointing. The drug was administered orally in doses up to tolerance both in ambulatory patients and in ward patients under close observation without demonstrable effect. This fits the experience recently reported by Crowley *et al.* (1950). Even when administered intravenously under controlled laboratory conditions, Priscoline had practically no effect upon the skin temperature in a patient with only moderately severe Raynaud's disease, while tibial nerve block directly afterward produced a maximal vasodilatation (Fig. 26). In a patient with only acrocyanosis, however, intravenous

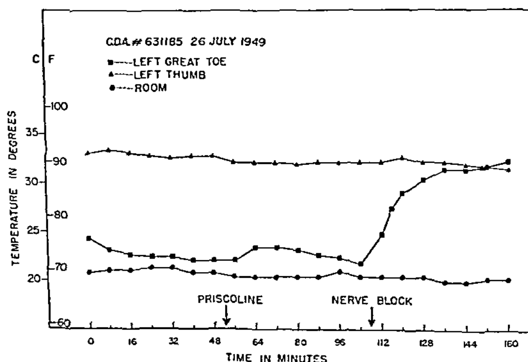


Fig. 26. The effect of Priscoline in a patient with mild Raynaud's disease.

The upper extremities had been denervated one year previously, the innervation of the lower extremities was intact. At first arrow, 75 mg of Priscoline were injected intravenously; at second arrow the left posterior tibial nerve was blocked with 1 per cent procaine. Note that, when administered in this manner, Priscoline had no effect upon the denervated upper extremity and had a trivial effect upon the lower extremity when compared with the effect of nerve block.

injection of the drug led to a very efficient vasodilatation (Fig. 27). It appears that vasodilators of this class are not effective in situations where their action is most needed. In addition, the same objection applies to

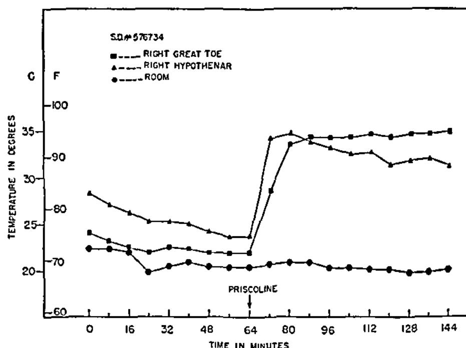


Fig. 27. The effect of Priscoline in a patient with mild acrocyanosis without evidence of organic occlusive vascular disease.
Note the prompt response of the skin temperature to maximal vasodilatation levels.

these as to vasodilators in general, namely, that as long as the effect is generalized they may do more harm than good by depriving a part with occlusive vascular disease of blood which might otherwise reach it. Drugs which induce vasodilatation would be more effective if they could be applied in such a way as to localize their actions.

Other Agents Which Block Adrenergic Activity. Longino *et al.* (1949) described the physiologic properties in man of a new drug, 2(N, p-tolyl-N [m'hydroxyphenyl] -aminoethyl)-imidazoline hydrochloride (C7337). This drug, Regitine, is closely related to Priscoline but lacks its direct contractile effects upon some smooth muscle. Like Priscoline, it may be administered orally or parenterally. They found the drug to be well tolerated, but a statement as to clinical usefulness must await further trial. Grimson, Longino, *et al.* (1949) used it satisfactorily in the management of a patient with pheochromocytoma.

Yohimbine, an alkaloid named after the West African tree from which it is derived, has been used as an aphrodisiac. Like the benzodioxanes, it

blocks the positive effects of adrenaline and of sympathetic nerve stimulation, but its actions are not so well known as are those of 933F (Hamet, 1925; Bacq, 1936*B*). Neither yohimbine nor its isomer, corynanthine, has found clinical application. For an excellent review of these and other less well known chemical substances which block the effects of adrenaline injection and adrenergic nerve stimulation, the reader is referred to that published recently by Nickerson (1949).

B. AGENTS BLOCKING CHOLINERGIC ACTION

In recent years a number of substances have been described which block the cholinergic effects of autonomic nerve stimulation. As in the case of adrenergic blocking agents, these, with few exceptions, have been more useful as tools in physiologic studies than in the clinic.

Atropine. This alkaloid of belladonna is the best known of these agents. It blocks, probably by competition for a common receptor substance, all the muscarine-like actions of parasympathetic nerve stimulation and of parasympathomimetic substances. Its effectiveness varies somewhat with different organs, being less effective in its ability to block the responses to vagal stimulation of the gastrointestinal tract than those to parasympathetic stimulation of the heart and salivary glands. Scopolamine has actions similar to those of atropine. Their applications in medicine and surgery are too many to describe here, and the reader is referred to the excellent description of these and other similar drugs by L. Goodman and Gilman (1941).

Curare. This substance in the crude and purified forms (Intocostrin) blocks the action of cholinergic nerve stimulation and of parasympathomimetic drugs at ganglionic synapses (Cannon and Rosenblueth, 1937) and at voluntary myoneural junctions. The block is effected by virtue of a rise in the threshold for responses to acetylcholine.

The drug has found clinical application in anesthesia in cases where muscle relaxation is desired without increasing the depth of anesthesia, and has been recommended as an aid in the management of the spastic phase of tetanus. Several disadvantages are inherent in its use (Godman and Adriani, 1949). Its usefulness for these purposes is still under investigation.

Tetraethylammonium Compounds. Quaternary ammonium compounds have been the subject of numerous investigations during the past five decades, but it was not until very recently that the principal action of the bromide of tetraethylammonium was demonstrated to be at the ganglionic synapse (Acheson and Moe, 1945 and 1946; Acheson and Pereira, 1946). To this property are attributed the hypotension, bradycardia, and peripheral vasodilatation which result from intramuscular and intravenous injections

injection of the drug led to a very efficient vasodilatation (Fig. 27). It appears that vasodilators of this class are not effective in situations where their action is most needed. In addition, the same objection applies to

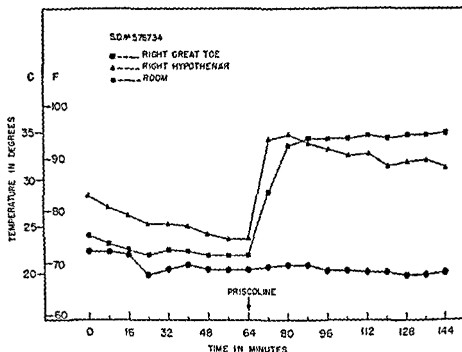


Fig. 27. The effect of Priscoline in a patient with mild acrocyanosis without evidence of organic occlusive vascular disease.

Note the prompt response of the skin temperature to maximal vasodilatation levels.

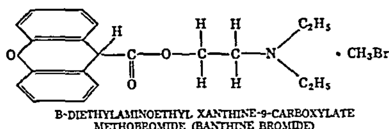
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lieved, however. One patient had a severe untoward reaction to the drug similar to the reaction observed in the patient treated with Priscoline.

Banthīne. This drug, like tetraethylammonium chloride, is another quaternary amine which blocks the transmission of nerve impulses at the ganglion. It is effective in blocking not only the nicotine-like action of acetylcholine and cholinergic nerve excitation but also the muscarine-like actions. As a secretory depressant and as an inhibitor of gastrointestinal



B-DIETHYLAMINOETHYL XANTHINE-9-CARBOXYLATE METHOBROMIDE (BANTHINE BROMIDE)

motility, it has been recommended for the treatment of peptic ulcer. In average doses it has produced only minor side effects.

Grimson, Lyons, and Reeves (1950) have recently reported their experience in 100 patients with peptic ulcer treated with Banthīne. Of these, 55 had ulcers of such a nature that they met the usual conservative indications for surgical intervention. Seven others had stomal ulcers. The usual dosage used was 100 mg orally four times a day. Of this group only 5 required gastrectomy. None of those with stomal ulcer required surgical intervention. From an experience with its use in 20 patients with peptic ulcer and 7 with other gastrointestinal complaints, C. H. Brown and Collins (1950) reported encouraging results. As side effects, they observed dryness of the mouth, visual disturbances, slowness of urination, constipation, and hoarseness. In both reports, the authors themselves point out that more time is necessary for proper evaluation of this form of therapy for peptic ulcer, but that the preliminary results appear promising.

Grimson, Lyons, Watkins, and Callaway (1950) have reported good results with the use of Banthīne for controlling hyperhidrosis. Early observations in 4 patients were reported as very favorable.

"SC 1950." Longino *et al.* (1949) reported a new quaternary amine (2,6 dimethyl, diethyl piperidinium bromide) which they have tested in animals and in man. The drug ("SC 1950"), unlike Banthīne, must be administered parenterally. In doses of 0.5 to 1.5 mg per kilogram of body weight, it lowers the blood pressure, blocks some autonomic reflexes, and reduces the motor and secretory activity of the stomach. Only minor side effects are produced by the drug, and it may prove to be a valuable adjunct

of the drug in man and animals. There are some minor effects which are of some interest. It has an inotropic effect upon the heart and a cholinergic effect upon the adrenals, so that moderate doses of the drug cause a liberation of adrenaline. This fact has been used as a diagnostic tool for pheochromocytoma (LaDue *et al.*, 1947; Bartels and Kingsley, 1948). When injected intra-arterially in the dog, it produces a vasoconstriction apparently by direct action upon the blood vessels. The drug does not block the action of pressor substances. In fact, it potentiates their actions (Page, 1949; Hoobler, Moe, and Lyons, 1949).

Following these observations by Acheson and his coworkers, the drug, especially the chloride marketed as Etamon Chloride (Parke, Davis & Company), was tested as an agent for producing "chemical sympathectomy" or "autonomic blockade" in doses of 350 to 500 mg in the adult injected intravenously or intramuscularly. Recent reports strengthened the hopes that this drug would produce peripheral vasodilatation equal to that resulting from procaine block or severance of the autonomic nerves (Berry *et al.*, 1946; Coller *et al.*, 1947; Hoobler, Malton, *et al.*, 1949). Comparable results were not obtained in other clinics, however (DeBakey *et al.*, 1947; Pearl, 1948*A*; Boyd *et al.*, 1948; Winsor, 1950). Our personal observations confirm these latter data. Even when marked hypotension was produced by the drug, it was usually possible to obtain a further rise in the skin temperature of the fifth finger when the ulnar nerve was blocked with procaine at the elbow or at the wrist.

While some good clinical results have been reported from the use of this drug not only in peripheral vascular disease but also in painful states of the extremities (Coller *et al.*, 1947), this experience has not been universal (Pearl, 1948*B*), and the drug is now seldom used as a peripheral vasodilator. The Hypertension Clinic at Massachusetts General Hospital found the drug impractical as a method for preoperative evaluation of hypertensive patients for sympathectomy, and use of the drug is not without risk (Friedlich *et al.*, 1948; Lasser *et al.*, 1949). Lannon and Braudo (1949) used Etamon Chloride for treating muscle spasm and the pain associated with it in poliomyelitis. They reported uniformly good to excellent results in all of the 25 patients they tested. Eiben (1950) treated 45 patients at City Hospital, Cleveland, with poliomyelitis and muscle spasm, using doses of 7 mg per kilogram of body weight intravenously or 20 mg per kilogram of body weight intramuscularly. He found significant relief in 70 per cent of the patients. In 60 per cent of them there was clear-cut relief of muscle spasm demonstrable by prompt improvement in the range of motion of the muscles previously in severe spasm. Spasm was never completely re-

VI. Vasodilator Drugs

In the preceding pages drugs have been described which experimentally, at least, have induced vasodilatation in normal blood vessels by interfering with one of the stages in the transmission of the nerve impulse to the smooth muscle of the blood vessel wall. A number of different drugs have been recommended as vasodilators by virtue of their direct action upon the smooth muscle of small blood vessels or other properties not directly connected with conduction or transmission of the nerve impulse.

Alcohol. This has long been recognized as one of the most effective vasodilators. Its direct action upon blood vessels is minimal, however, and it acts, for the most part, by central inhibition of vasoconstrictor tone. This drug is used very widely in peripheral vascular disease. Alcohol affects the vessels of the face and hands more than those of the feet (Stewart, 1915; Cook and Brown, 1932; Horton *et al.*, 1936; Abramson *et al.*, 1941). When there is severe occlusive disease of the arteries in the lower extremities with relatively little elsewhere, therefore, it is possible that the circulation in the feet may actually worsen after the administration of alcohol.

One would expect it to be very useful in conditions where spasm is present from vasomotor overactivity. Where ischemia is due to organic occlusion, however, improvement is probably subjective only. The drug is administered orally in palatable form or may be administered intravenously.

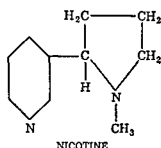
Ether. The vasodilator action of ether anesthesia is described below (p. 158). For the most part, this effect is a central one, but the agent has a lesser direct vasodilator action as well. R. A. Katz (1946) has described excellent results with the use of intravenous ether in severe peripheral vascular disease. The technique was tried at the Massachusetts General Hospital, but it was found ineffective. The recent report of Weisman and Allen (1950) confirms this latter experience.

Amyl Nitrite. This volatile nitrite has a direct relaxing action on smooth muscle of the small blood vessels and of hollow organs. It has been used to differentiate between functional spasm and organic obstruction at the ampulla of Vater. Atropine does not block the antispasmodic activity of the drug. While inhalation of the drug produces a well-known hypotension and facial blush, it has less effect upon the circulation of the hands and still less upon that of the feet. Amyl nitrite acts very transiently. The longer-acting sodium nitrite exerts its effects upon the venules and capillaries beyond the arterioles (Weiss *et al.*, 1937) and may actually produce arteriolar constriction in man in the erect position (Wilkins *et al.*, 1937). It is not useful as a vasodilator in peripheral vascular disease.

in the treatment of gastrointestinal diseases. The drug does not produce as much release of vasomotor activity as does ganglionectomy, however (Winsor, 1950).

Other Substituted Ammonium Compounds. There has been considerable interest recently in the ganglion-blocking properties of certain bistrimethylammonium salts, the iodides and bromides. Hypotensive and vasodilator effects have been demonstrated for pentamethonium iodide (P. Arnold and Rosenheim, 1949; Arnold, Goetz, and Rosenheim, 1949; Grob *et al.*, 1949) and for hexamethonium iodide (Finnerty and Freis, 1950). These compounds appear to act by blocking transmission of nerve impulses at ganglionic synapses, both sympathetic and parasympathetic. Hexamethonium was found to be a more powerful agent than either Priscoline or Etamon Chloride for inducing a rise in skin temperature in man. Side effects were minimal except for a postural hypotension. Neither the hexamethonium nor the pentamethonium salts possess the curarizing properties shown by some of the higher members of the series (decamethonium) and, in fact, may be used as antidotes for them (A. R. Hunter, 1950). These compounds do not block or reverse the action of adrenaline. An opinion of their clinical value must await further study of their pharmacological properties.

Nicotine. Nicotine is a liquid alkaloid isolated from the tobacco leaf. Much of the early work on the physiology and anatomy of sympathetic ganglia was done with the aid of this drug (Langley and Dickinson, 1889; Langley, 1901*A*). After preliminary excitation, it blocks transmission at the synapse, so that the preganglionic nerve impulse fails to excite the postganglionic neuron, which itself remains responsive to direct stimulation. It was therefore possible by means of this drug to determine the site at which preganglionic fibers synapsed with their postganglionic neurons. Nicotine exerts its action not only upon sympathetic ganglia but upon parasympathetic ganglia too. As one would expect from the many similarities between the ganglionic synapses and the myoneural junction in striated muscle, nicotine also blocks the effect of nerve stimulation and of acetylcholine, acetyl-beta methylcholine, and carbaminoylcholine upon skeletal muscle. As in the case of other blocking agents, the drug does not abolish the liberation of the chemical mediator. Nicotine has been of inestimable value in the laboratory for clarification of the organization and function of the autonomic nervous system. It is a useful toxicologic agent, especially in agriculture, but it has no clinical application.



NICOTINE

VI. Vasodilator Drugs

In the preceding pages drugs have been described which experimentally, at least, have induced vasodilatation in normal blood vessels by interfering with one of the stages in the transmission of the nerve impulse to the smooth muscle of the blood vessel wall. A number of different drugs have been recommended as vasodilators by virtue of their direct action upon the smooth muscle of small blood vessels or other properties not directly connected with conduction or transmission of the nerve impulse.

Alcohol. This has long been recognized as one of the most effective vasodilators. Its direct action upon blood vessels is minimal, however, and it acts, for the most part, by central inhibition of vasoconstrictor tone. This drug is used very widely in peripheral vascular disease. Alcohol affects the vessels of the face and hands more than those of the feet (Stewart, 1915; Cook and Brown, 1932; Horton *et al.*, 1936; Abramson *et al.*, 1941). When there is severe occlusive disease of the arteries in the lower extremities with relatively little elsewhere, therefore, it is possible that the circulation in the feet may actually worsen after the administration of alcohol.

One would expect it to be very useful in conditions where spasm is present from vasomotor overactivity. Where ischemia is due to organic occlusion, however, improvement is probably subjective only. The drug is administered orally in palatable form or may be administered intravenously.

Ether. The vasodilator action of ether anesthesia is described below (p. 158). For the most part, this effect is a central one, but the agent has a lesser direct vasodilator action as well. R. A. Katz (1946) has described excellent results with the use of intravenous ether in severe peripheral vascular disease. The technique was tried at the Massachusetts General Hospital, but it was found ineffective. The recent report of Weisman and Allen (1950) confirms this latter experience.

Amyl Nitrite. This volatile nitrite has a direct relaxing action on smooth muscle of the small blood vessels and of hollow organs. It has been used to differentiate between functional spasm and organic obstruction at the ampulla of Vater. Atropine does not block the antispasmodic activity of the drug. While inhalation of the drug produces a well-known hypotension and facial blush, it has less effect upon the circulation of the hands and still less upon that of the feet. Amyl nitrite acts very transiently. The longer-acting sodium nitrite exerts its effects upon the venules and capillaries beyond the arterioles (Weiss *et al.*, 1937) and may actually produce arteriolar constriction in man in the erect position (Wilkins *et al.*, 1937). It is not useful as a vasodilator in peripheral vascular disease.

Papaverine. This opium derivative was found by Pal (1930) to have a direct dilating action on blood vessels. More recently there have been several reports describing the vasodilator action of papaverine in man with rather conflicting results (cf. Abramson and Ferris, 1940). Mulinos *et al.* (1939) found the drug useful in Raynaud's disease, but Littauer and Wright (1939) reported it to be of questionable value in peripheral vascular disease. While the vasodilating effect of papaverine is certainly not spectacular, it may have enough of an effect to make it worth while using in conjunction with other measures in the treatment of peripheral vascular disease where organic occlusion is not severe. The drug should be administered intramuscularly or intravenously in doses of 50 to 100 mg if therapeutic effects are to be obtained.

Histamine. T. Lewis and Grant (1924) observed capillary dilatation, relaxation of arteriolar tone, and wheal formation due to increased capillary permeability when histamine was injected subcutaneously. This is commonly referred to as the "triple response" to histamine or to noxious excitation of the skin. Weiss *et al.* (1932) observed similar effects when histamine was injected intravenously in man. Dilatation of the small blood vessels of the skin was also noted when the drug was administered locally by iontophoresis (Kling and Sashin, 1937). When injected directly into an artery, histamine produces an intense vasodilatation of the small blood vessels distally (E. V. Allen and Crisler, 1937). This fact has stimulated the intra-arterial injection of the drug for treating organic peripheral vascular insufficiency (thromboangiitis and arteriosclerosis), but little benefit has been achieved by this type of treatment. Iontophoresis with histamine can be accomplished by using solutions of the drug in 1:1,000 dilution. When injected intravenously or preferably intra-arterially, doses of 0.1 to 0.2 mg of histamine result in a temporary vasodilatation in the periphery. The effect, however, is too short lasting to be clinically useful.

In 1937 Holtz and Heise reported that histamine could be produced in vitro by the action of ascorbic acid and sulfhydryl compounds on histidine. Later, Holtz and Credner (1944) demonstrated the production of histamine from histidine in the guinea pig. These observations were transposed to man, and good results were reported from the use of histidine and ascorbic acid in peripheral vascular disease (Wirtschafter and Widmann, 1947; Friedell *et al.*, 1948). It should be pointed out, however, that the biochemical aspects of histamine liberation under these circumstances have not been checked, and the reported beneficial effects in peripheral vascular disease have not been confirmed (Weisman and Allen, 1950).

Nicotinic Acid. In a study of the effects of nicotinic acid and related compounds upon the skin temperature, Bean and Spies (1940) confirmed their earlier observations that nicotinic acid produces a vasodilatation in the skin, especially of the head and neck. There is variability in the peripheral vascular responses to nicotinic acid from significant increases in blood flow (Abramson, Katzenstein *et al.*, 1940), to equivocal results (Popkin, 1939), to no significant effects (Crowley *et al.*, 1950). Clinically, the drug has been used quite extensively, but no objective data are available for an evaluation of its effectiveness. It may be taken orally in doses of 100 mg four to six times a day.

Other Vasodilators. The action of *Priscoline* as a blocking agent against adrenergic effects has been described above. In addition, there is evidence that it may produce vasodilatation by direct action on blood vessels when injected intra-arterially (Meier and Meyer, 1941). Some promising results have been observed when the drug was administered intra-arterially (Lynn, 1950) in peripheral vascular disease, but this method has not been employed widely.

Dogliotti (1949) is reported to have used *curare* in doses of "20 to 40 units" by intra-arterial injection in the treatment of thromboangiitis and arteriosclerotic disease of the vessels of the extremities. Of 46 cases with peripheral vascular disease, 22 showed "almost a complete disappearance of clinical symptoms." Only 7 of the 46 cases showed no improvement. The mechanism of this action is not entirely clear and needs confirmation and further study.

Impressed by the prompt clinical improvement observed in patients with coronary heart disease after the administration of *heparin* and *Dicumarol*, Gilbert and Nalefski (1949) studied the acute effects of these agents upon the coronary circulation. Both, Dicumarol more than heparin, caused a striking increase in the rate of blood flow through the coronary sinus.

Krayer, Moe, and Mendez (1944) observed that femoral vasodilatation resulted in the dog when as little as 0.5 microgram of *protoveratrine* per kilogram of body weight was injected. The vasodilatation was central in origin and not due to a direct effect upon the peripheral vessels. This and related drugs are being studied for their usefulness in the treatment of hypertension (Meilman and Krayer, 1949; Wilkins *et al.*, 1949; Wilkins, 1950, Currens *et al.*, 1951). It has not been used in peripheral vascular disease. *Tissue extracts* have been used at various times for their supposed vasodilator effects. The most widely known of these are Padutin and Depropanex, preparations from pancreatic extract believed to have a

specific vasodilator hormone and other beneficial properties (Leschke, 1930; Frey, 1931; Roth *et al.*, 1933; Prochnow, 1933; Wolffe, 1939). As de Takats *et al.* (1939) stated, however, observations regarding the effectiveness of Padutin and Depropanex need careful control and, in fact, any improvement may be attributed to the course of the disease or to a nonspecific effect of the drugs. Most recently, Martorell (1948) has recommended the use of splenic extracts in arteriosclerotic disease on the basis of their hypoglycemic, hypocholesterinemic, lipotropic, vasodilating, and hypotensive actions.

VII. The Use of Drugs in Diseases of the Peripheral Circulation

It is apparent from the foregoing pages that a host of drugs have been tested in both the laboratory and clinic in the hope that they would be useful in the treatment of diseases of the circulation. Drugs have been used which impede vasoconstrictor activity at all points in the hierarchy of centers controlling the peripheral effector. In this group may be included ether, alcohol, and agents like typhoid vaccine. Tetraethylammonium chloride (Etamon Chloride) is representative of the group of drugs which interrupt vasoconstrictor activity at the ganglionic synapse; the dihydrogenated ergot alkaloids, the benzodioxanes, dibenamine, and Priscoline are characteristic of those which block the positive action of adrenaline and of sympathetic impulses at the level of the effector. They must be used with caution (Simeone and Sarnoff, 1947; Friedlich *et al.*, 1948; Lasser *et al.*, 1949) because of their side effects. Most of these agents have had clinical trial in peripheral vascular disease and enthusiastic reports support their use. In each case, however, there is evidence to the contrary, and this has been presented above.

It is reasonable to expect improvement of the circulation when these drugs are administered for conditions in which functional spasm is the major problem. They become relatively ineffective, however, when there is even slight organic involvement (Figs. 26 and 28). In the presence of severe occlusive disease of the lower extremities the use of vasodilator drugs may actually be contraindicated, especially in elderly individuals. If a drop in blood pressure is produced by the drug when the heart is unable to compensate for vasodilatation elsewhere in the body by increasing its output, then the circulation in the diseased parts may actually become worse than before the drug was administered. Some of the drugs, such as acetylcholine, histamine, and Priscoline, have been injected intra-arterially in order to produce a local effect. This procedure may be useful in acute situations,

but one should hesitate to use it repeatedly for fear of damage to the injected artery. It would seem preferable to attempt to improve the oxygen utilization of tissues by the administration of substances such as cytochrome C (Proger and Dekaneas, 1946*A* and *B*) than to try to improve the circulation by means of drugs which have generalized vasodilator effects.

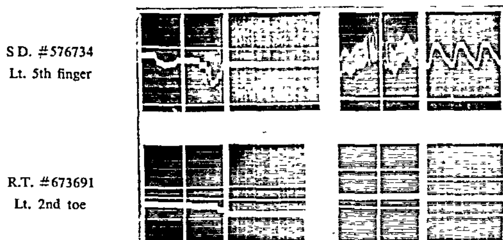


Fig. 28. Plethysmograph (Burch-Winsor) records of pulse volumes in a patient with acrocyanosis without organic vascular disease (S.D.) and in a patient with severe thromboangiitis obliterans (R.L.) in an environmental temperature of 20° C.

The first of each pair of records is slow speed, the second is fast speed. In neither case was the pulse wave discernible before Priscoline. After Priscoline, the pulse wave measured about 12 cu mm per 5 cc of part in S.D., but it remained undiscernible in R.L.

None of the drugs which act to block the activity of adrenergic nerve fibers or the transmission of the nerve impulse in sympathetic ganglia has been found as effective as block or excision of the adrenergic nerves themselves. Sympathectomy and, to a lesser extent, sympathetic block with procaine, alcohol, or phenol (Haxton, 1949) have the advantages of localization of the vasodilator effect and of at least approaching completeness of the desired effect (DeBakey *et al.*, 1947; Winsor, 1950).

CHAPTER VI

*Physiology of Visceral Pain**

According to Langley, "the autonomic nervous system consists of the nerve cells and nerve fibres by means of which efferent impulses pass to tissues other than multi-nuclear striated muscle." Thus, by strict definition, the parasympathetic and sympathetic nerves, which arise from the brain stem and the thoracolumbar and sacral portions of the spinal cord, are purely motor in function and control homeostasis. The fact that apparently all forms of visceral pain can be relieved by sympathectomy does not fit into this concept, but the paradox has been explained in the past thirty years by improved anatomical and physiological methods and suitable stimulation of human volunteers. These investigations have shown that afferent nerve fibers, which differ in no way from those in a sensory nerve to the skin, run in the cardiac, splanchnic, and other sympathetic trunks. The fibers differ from the classical autonomic axons in having no synapses in the peripheral ganglia and in entering the spinal cord over its posterior roots (see Chap. III). The undifferentiated endings of the viscerosensory fibers are identical with those found in the skin and cornea. These were illustrated in Stöhr's monograph (1928), but it has only recently been appreciated that they are the receptor endings for superficial and deep pain (W. E. LeG. Clark, 1947) as well. The Vater-Pacinian corpuscles that are found throughout the mesenteries have been studied by Sheehan (1932) and their degeneration has been observed after section of the splanchnic nerves. It therefore appears that viscerosensory and cutaneosensory fibers are identical both in histological characteristics and in electrical conduction. For the purpose of clarity, therefore, afferent axons from the internal organs will be referred to as the viscerosensory fibers, in contrast to the true autonomic or visceromotor fibers of Gaskell and Langley. Contrary to current opinion, Langley (1903) was well aware of the afferent fibers to the viscera in the craniosacral and sympathetic pathways. He regarded these as belonging to the somatic system He also realized that their number was relatively small and that therefore the threshold of visceral sensation was

* Two particularly valuable symposia on this subject have been presented by the Association for Research in Nervous and Mental Disease on sensation (1935) and pain (1943)

high. It is of interest in this respect to quote Langley's ideas on this important matter: * "All that seems to me possible at present toward arranging afferent fibres into autonomic and somatic divisions is to consider as afferent autonomic fibres those which give rise to reflexes in autonomic tissues, and which are incapable of directly giving rise to sensation; and to consider all other afferent fibres as somatic . . . since the vagus, the pelvic nerve, and every white ramus of the sympathetic can give rise to pain."

A thorough understanding of the visceral sensory pathways is of the greatest practical importance to the neurosurgeon interested in the control of pain. The approach to this subject has been far from easy, not only because the objective study of pain by laboratory experiment is difficult, but also because of early theories which, by very strength of tradition, have stood in the way of progress. For these reasons the exposition of present concepts of pain in visceral disease forms a most important chapter in this book.

The relative insensibility of the viscera is common knowledge. William Harvey (quoted by Goltz, 1863) observed that touching the exposed human heart failed to arouse the slightest sensation (see p. 256). By animal experiments von Haller (1760) first established the insensibility of the visceral pericardium, pleura, and peritoneum to mechanical stimulation. After the advent of local anesthesia Lennander (1901) went so far as to state categorically that the viscera were wholly insensitive, and that only traction or irritation of the parietal peritoneum could arouse painful sensations

Progress in the study of visceral pain followed the discovery of the "adequate stimulus." According to Sheehan (1936), the first conception of this idea is to be found in the writings of Whytt (1751), but it then passed into oblivion for another century and a half. The experiments of Hurst (1911), Schrager and Ivy (1928), and Davis, Pollock, and Stone (1932) have demonstrated that distention of any hollow viscus is painful; Ryle (1926, 1928) amplified Hurst's concept by emphasizing contraction of smooth muscle in the hollow viscera as an adequate physiological stimulus. In addition, the importance of the chemical products of exercising muscle in the presence of a deficient blood and oxygen supply has been ably set forth by Sutton and Lueth (1930) and by R. M. Moore (1938). Frequent operative reports have pointed out that pain results from crushing arteries (Leriche, 1927*B*; W. K. Livingston, 1930), while Odermatt (1922) and Spiegel and Wassermann (1926) have produced pain by distending the

* Langley, J. N. "The autonomic nervous system." *Brain*, London, 1903, 26: 1–26.

larger arteries. Sudden distention or strong contraction of any part of the gastrointestinal or genitourinary tracts, rapid stretching of the capsule of such solid viscera as the liver and spleen, and abrupt anoxemia of the cardiac musculature are now recognized as the causes of pain in visceral disease.

Early theories avoided the possibility of direct pain transmission in three ways:

First, by assuming that violent contractions of the abdominal viscera must cause traction on the mesentery and therefore pull on the somatic nerves in the parietal peritoneum (Lennander, 1901).

Second, that some form of afferent impulse, but not true pain, travels up the splanchnic and other visceral nerves as far as the posterior horn of the spinal cord. There the bombardment of visceral impulses sets up an irritable focus * and diminishes the threshold for the somatic sensory impulses which are constantly entering the same segment of the cord from the periphery of the body. Normal subconscious impulses are thus magnified to actual pain. This is referred by the patient to cutaneous areas (Head zones) which share a common segmental spinal innervation with the diseased viscus (Fig. 29). It is of historical significance that Head (1893), who first made a careful study of the segmental levels to which visceral pain is referred, pointed out the interesting fact that "the sensory distribution of the sympathetic" corresponds with Edgeworth's (1892) chart of the sympathetic rami which carry large (sensory) axons and also "follow the lines laid down by Gaskell (1886) for the course of the motor and inhibitor fibres."

It is unfortunate that Mackenzie (1893 and 1924), who was such a prolific writer, insisted that the viscerocutaneous theory accounted for all forms of visceral pain. It did explain in a superficially plausible way the reference of pain to areas distant from the underlying inflamed organ (e.g., the pain in the right scapular region which is so often felt in gall-bladder disease, the inguinal and testicular pain of renal colic, and the pain which radiates down the arm in angina pectoris). The demonstration by Weiss and Davis (1928) that simple procainization of the skin in the areas of referred pain is sufficient to cause its relief was supposed to have confirmed this hypothesis. However, as these authors pointed out,

* This so-called "irritable focus" is not a satisfactory physiological concept. Mackenzie (1912) stated that "this stimulus [from the diseased organ] may be of the kind that affects neighboring nerve cells, and these nerve cells react according to their functions. When such stimulation affects a sensory nerve, pain arises, which is referred to the peripheral distribution of the nerve so stimulated." For a more satisfactory neurophysiological interpretation of the "irritable focus," see the paper by Hinsey and Phillips (1940).

a dull, deep form of pain may persist after complete cutaneous anesthesia and, with suitable stimuli, pain will nearly always break through (see below).

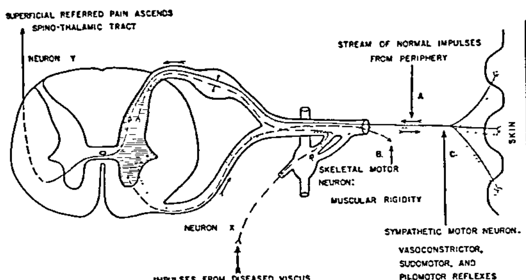


Fig. 29. Diagram to illustrate Mackenzie's theory of referred pain.

Afferent impulses from a diseased viscus enter the posterior horn of the spinal gray matter over neuron X and set up the "irritable focus" (shaded area). The normally subconscious afferent impulses from the body surface which traverse neuron A now jump the synapse to neuron Y and reach the thalamus as pain which is referred to characteristic cutaneous areas. The motor neurons B and C may also be discharged and cause reflex rigidity of skeletal muscle, or vasomotor, sudomotor, and pilomotor phenomena.

Morley (1931), in his book on abdominal pain, stated that pain from the internal organs is never accurately localized on the surface of the body nor accompanied by deep tenderness or reflex rigidity of muscle until the disease process has spread to the parietal peritoneum. Instead of a viscerocutaneous spread of referred pain, he substituted the idea of a peritoneocutaneous mechanism. The Manchester surgeon concluded that well-localized superficial pain arises only from irritation of nerves which are sensitive to those stimuli that produce pain when applied to the surface of the body. As evidence for this he pointed out that when pain is referred to a clearly defined point from a gastric ulcer, inflamed gall bladder, or acute appendix, the inflammatory process has always spread to the parietal peritoneum. This concept is a distinct aid in the explanation of referred pain in certain diseases of the peritoneal and pleural cavities, but it cannot account for such forms of referred pain as are seen in angina pectoris, where there is no inflammatory process and there is no direct contact of the heart with the intercostal nerves.

A *third* possible mechanism of visceral pain has been described by Davis and Pollock (1932). As a result of observations made by Langley (1921) and by Ranson and Billingsley (1918), it is commonly supposed that there are no sensory fibers traversing the superior cervical sympathetic ganglion,* yet stimulation of this structure is often painful. This pain is relieved only by section of the trigeminal and the upper cervical posterior roots. Davis and Pollock therefore concluded that stimulation of this ganglion produces pain through sympathetic motor impulses to the skin and blood vessels of the face. They hazard the guess that the pain might be due to the liberation of a metabolite, which in turn stimulates the ordinary sensory endings of the somatic nerves. This is in line with Lindgren and Olivecrona's (1947) demonstration that residual radiation of anginal pain to the lower jaw after cervicothoracic denervation of the heart is relieved by blocking the mandibular nerve (see p. 269).

The evolution of current concepts of visceral pain is of historical as well as practical interest. It was recognized from the beginning by both J. Ross (1888) and Head (1893) that, in addition to the superficial referred "somatic" pain, there is frequently a deep-seated distress, a deep, heavy "splanchnic" pain felt in the region of the diseased organ. In Ross' words: †

> Disease of an internal organ—say the stomach—is accompanied by pain over the seat of the organ—the epigastrium in the case of the stomach—a pain that may be regarded as of splanchnic origin and named accordingly the splanchnic pain. In addition to this pain, the patient complains of pain between the shoulders and in front of the chest. . . . The splanchnic nerves of the stomach are derived from the fourth and fifth, and probably the sixth dorsal nerves, and when the splanchnic peripheral terminations of these nerves are irritated the irritation is conducted to the posterior roots of the nerves, and on reaching the grey matter of the posterior horns it diffuses to the roots of the corresponding somatic nerves and thus causes an associated pain in the territory of distribution of these nerves, which may appropriately be named the somatic pain.

It was Ross who first suggested the idea of an "irritable focus" in the cord, but Mackenzie, in incorporating this valuable concept into his theory, disowned the idea of direct visceral sensation. In essential agreement with Ross, Head explained the known facts so well that his words deserve to be quoted at length: ‡

* Heinbecker (1932) observed large myelinated fibers with the characteristic conduction rate of afferent sensory axons in the upper portion of the cervical sympathetic trunk, but he stated that they enter the vagus.

† Ross, J. "On the segmental distribution of sensory disorders" *Brain*, London, 1888, **10**: 333–361.

‡ Head, H "On disturbances of sensation with especial reference to the pain of visceral disease." *Brain*, London, 1893, **16**: 1–133.

> Thus, as our viscera are so notoriously insensitive, and as we have never had the opportunity of developing the sense of localisation in them, owing to their inaccessibility to touch, it is not to be wondered at that the maximum pain is not felt in the organ affected. . . . A painful stimulus to an internal organ is conducted to that segment of the cord from which its sensory nerves are given off. There it comes into close connection with the fibres for painful sensation from the surface of the body which also arose from the same segment. But the sensory and localising power of the surface of the body is enormously in excess of that of the viscera, and thus by what might be called a psychical error of judgment the diffusion area is accepted by consciousness, and the pain is referred on to the surface of the body instead of on to the organ actually affected. I do not mean to state that pain is never referred to the organ affected. Far from it. The pain is frequently felt in the organ itself, but it is "dull," "heavy," "wearing," and not "sharp," "aching," "stabbing," like the referred pain.

Evidence today that deep splanchnic pain is conducted directly to the sensorium is so clear cut that it deserves little further discussion. If that portion of Mackenzie's theory were correct which attempted to explain the phenomena of reference, it should follow that these manifestations could be abolished after interruption of afferent nerves from the cutaneous area. Recent data prove that this is not the case. Although it has been subscribed to by C. M. Jones and Chapman (1942), Wolf, Wolff, and Goodell (1947) have been unable to confirm the crucial experiment of Weiss and Davis, cited above, that pain from balloon distention of the duodenum is interrupted by procainization of the abdominal wall. Boyden and Rigler (1934) have likewise noted the persistence of deep pain under an anesthetized area when the interior of the duodenum is stimulated with a faradic current.

Further evidence against Mackenzie's doctrine was presented by T. Lewis (1942) who "failed to alter, in the least, anginal pain in an eminently suitable patient in whom the referred pain was focused over the sternum and could be provoked, with regularity and by a constant amount of effort, both before and after thoroughly anesthetising the affected part of the body wall." Cohen and H. W. Jones (1943) have reported reference of anginal pain to a phantom arm after amputation. Various other observers have produced classic "referred" pain on stimulation and found that it was still present after thorough infiltration of procaine into the superficial area of reference: viz., shoulder area on stimulation of the diaphragm (W. K. Livingston, 1938*A*), and of the nerve itself in the course of phrenicectomy (Woollard, Roberts, and Carmichael, 1932); loin and groin on ureteral distention (A. M. McLellan and Goodell, 1943); and the observations on mechanical stimulation of the inflamed appendix and penetrating duodenal ulcers by Kinsella and Bentley cited below.

In animals, evidence of pain is still clearly evoked by distention of the gall bladder (Davis, Pollock, and Stone, 1932) or by ischemia of the myocardium (White, Garrey, and Atkins, 1933) after desensitizing the thoracic wall by cutting the intercostal nerves peripheral to the point of origin of the sympathetic rami communicantes, although it is abolished by cutting the splanchnic or cardiac nerves, or by cutting the corresponding thoracic posterior spinal roots.

Experiments have been reported by Lewis and Kellgren (1939) which bring out the fundamental similarity in the conduction of painful stimuli from all the deeper portions of the body, regardless of whether they originate in a viscus, or in the ligamentous structures, or in the deeper layers of skeletal muscle. By injecting hypertonic saline into an upper thoracic interspinous ligament * or the belly of the rectus abdominis muscle, these investigators found it possible to provoke pains with accompanying subjective sensations and visceromotor reflexes that are indistinguishable in quality from, as well as similar in distribution to, those of angina pectoris or abdominal colic. From these observations they have drawn the conclusion that "there is no special form of pain, referred or otherwise, and no special viscerosensory or visceromotor reflex, which is the hallmark of visceral disease." In addition, Lewis and Kellgren point out that deep somatic and visceral structures are supplied by a common set of afferent nerves (including pain fibers) and that this common system is responsible for all the pain and referred phenomena of visceral disease.

In the light of present theories on sensory endings and their conducting fibers made in the anatomical laboratories at Oxford by Feindel, Weddell, and Sinclair (1948), it is evident that visceral innervation differs in a quantitative rather than a qualitative manner from that of other deep somatic structures such as periosteum, fascia, and skeletal muscle. The accuracy with which painful stimuli in these areas can be appreciated depends on the quantity and interweaving of the pain fibers (Weddell, 1945). In periosteum, where many undifferentiated pain receptors overlap, there is a low sensory threshold with fairly accurate localization In muscle, with its greater paucity of afferent supply, the threshold is high unless the muscle is inflamed, and localization is notoriously poor. The same is true for the viscera, where sensory endings are scarce and difficult to find (Carpenter, 1918). It is even possible, as Sinclair, Weddell, and Feindel (1948) have suggested, that long-branched sensory axons supply viscera, deep struc-

* Further study of this experiment by Weddell *et al* (1948) has made it evident that the needle must have slipped to the side of the ligament and that the actual structure stimulated was the posterior division of a spinal nerve.

tures like muscle, and skin in common, so that pain of visceral origin can readily be interpreted as coming from somatic structures.

Sinclair, Weddell, and Feindel (1948) have recently reinvestigated the hypothesis of Davis and Pollock (1932), referred to above, that certain "referred" phenomena are produced by the formation of painful metabolites in the skin and underlying tissues. They conclude that * "there are two main mechanisms at work; the first of these is the misrepresentation by the central receiving apparatus of the source of the painful impulses, and the second is the production in the periphery, as the result of antidromic impulses, of metabolites which at first stimulate the nerve endings there and later damage them. It is probable that the operation of the first of these mechanisms gives rise chiefly to referred *pain,* while the chief result of the operation of the second is referred *tenderness.* . . ." This latter process may also account for cutaneous hyperalgesia and muscular rigidity, which can both be eliminated by procaine infiltration.

Further light on the conduction of visceral pain has been derived from direct stimulation or destruction of the sympathetic trunks in man. For example, Bentley and Smithwick (1940) carried out a series of experiments in the Massachusetts General Hospital on patients before and after bilateral resection of the splanchnic nerves and the lower thoracic and first lumbar ganglia for essential hypertension. Epigastric pain produced by insufflation of a balloon in the duodenum to a certain pressure disappeared to the right of the mid-line after a right-sided denervation, and the same degree of distention was no longer felt after bilateral operation. Adson (1935) and Leriche (1937*A*) have stimulated the splanchnic nerves in the course of operations under spinal anesthesia. In Adson's case, stimulation of the major splanchnic nerve produced pain near the upper part of the scapula, whereas the pain from the minor splanchnic was referred to the lower angle of the scapula. When the celiac ganglion was stimulated the patient noted pain in the shoulder, but when the peripheral fibers of the ganglion were pinched he described an aching sensation in the lower abdomen. White and Sweet (1952) have recently repeated these experiments under local anesthesia. Under these circumstances pain produced by stimulation of a major splanchnic nerve is referred to the corresponding upper abdominal quadrant; that from stimulation of the lumbar ganglia to the lower abdomen (L1 or L2) and pelvis (L3). Simeone, in the Massachusetts General Hospital, has also confirmed the reference of pain to the epigastric area in 2 cases of major splanchnic stimulation. The probable

* Sinclair, D. C., Weddell, G., and Feindel, W. H. "Referred pain and associated phenomena." *Brain,* London, 1948, 71: 184-212.

reason for the peculiarly high reference in the observations of Adson and Leriche is that, under spinal anesthesia, the lower sensory spinal rootlets of the splanchnic trunks were blocked by the drug, with only the higher connections (T4 to T6) remaining intact.

Leriche and Fontaine (1929*B*) have also stimulated the stellate ganglion in the course of operation on patients with angina pectoris. The patients invariably complained of a sense of oppression deep down in the chest around the region of the heart. Additional data on the direct investigation of visceral sensation in man have been reported by Learmonth (1931*C*), who recorded that a patient under low spinal anesthesia referred pain quite accurately to his bladder when the superior hypogastric plexus was crushed in the course of a presacral neurectomy.

In striking contrast to Lennander's (1901) finding that normal viscera are insensitive to crushing and other mechanical stimuli are observations made on inflamed abdominal organs. In these circumstances the normal high threshold of pain sensation is lowered to such an extent that touching gastric mucosa through a fistulous opening after irritation with mustard caused distinct discomfort (Wolf and Wolff, 1943*A*). Dragstedt and Palmer (1932) first observed the fact that mechanical stimulation of a duodenal ulcer at laparotomy under local anesthesia produced pain similar to ulcer distress. In the course of laparotomies under abdominal field block, Kinsella (1948) observed that digital compression of the inflamed appendix resulted in a right lower quadrant pain. Bentley (1948), who stimulated a number of penetrating duodenal ulcers, obtained clear-cut abdominal pain. This sensation was present despite complete anesthesia of the abdominal wall, but it disappeared after splanchnic block.

We have always insisted that visceral innervation is supplied by mixed nerves with distinct sympathetic or parasympathetic motor and somatic afferent components. In Lewis's (1942) words, "there is no physiological sanction for regarding the pain nerves of the sympathetic nervous system as distinct from those supplying deep-lying somatic structures. . . ." Physiologically and anatomically, Lewis believed them to be alike, and the fact that those of somatic origin at first use the channel of the spinal nerves, and those from visceral structures at first use the channel of the sympathetic system before entering the spinal roots is really immaterial.

Läwen (1923) was the first to use selective paravertebral procaine block of the sympathetic rami and ganglia in the study of the segmental innervation of the viscera. His observations have been corroborated and amplified by surgeons who have resected these structures. The monographs of Servelle (1942) and Luzuy (1946) give an interesting description of the

conditions in which sensory conduction of the splanchnic and thoracic sympathetic rami has been tested and of the great value of diagnostic procaine block in the experimental study of human pain.

Careful observation of the area to which pain is referred may be of the greatest value in the diagnosis of visceral disease. Not only should the patient be asked to give an accurate description of the areas to which his pain is referred, but careful examination should be made to map out areas of hyperesthesia, muscle spasm, abnormal sweating or vasomotor changes, and areas of increased pilomotor activity. If these correspond to definite dermatomes, the source of the pain is likely to be limited to certain organs. It is, however, impossible to differentiate between pain induced by distention of the common bile duct and that evoked by similar stimulation of the duodenum (Chapman, Herrera, and Jones, 1949). It is also of interest that irritation of the posterior roots which supply the splanchnic nerve may give rise to symptoms simulating visceral disease. We have seen two patients erroneously diagnosed as having cholecystitis, in one of whom the gall bladder had been removed, because of neurofibroma attached to the seventh and eighth spinal roots on the right side.

Table II has been compiled from all available data to show the afferent sensory pathways from the various viscera. It is noteworthy that, with the exception of the lower colon, bladder, prostate, and uterine cervix, these all enter the cord between the first thoracic and the upper lumbar segments. There is a good anatomical reason for this, inasmuch as no white sympathetic rami are present in the cervical and lowest lumbar segments of the cord In the following chapters it will be shown that interruption of the appropriate sympathetic rami or ganglia, either by resection or by chemical destruction, can be counted on to abolish visceral pain. The strategic point at which to interrupt the visceral afferent fibers is where their axons are concentrated in the paravertebral sympathetic ganglia or the corresponding posterior roots. Distal to the ganglia the nerves ramify widely, following the course of the visceral arteries. Surgical interruption at this level, such as pericoronary neurectomy recommended by Fauteux (1946), seems to us totally illogical. Not only are fibers likely to be missed, but axons are likely to regenerate, because only a short length can be resected.

The exact course of visceral pain fibers after they enter the spinal cord has not been accurately determined. Ranson (1947) has stated that, although unilateral section of an anterolateral column results in analgesia of the skin, muscles, fasciae, tendons, and bones, bilateral section is necessary to abolish visceral pain. Davis, Hart, and Crain (1929) have

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shown that distention of the gall bladder in dogs is still painful after complete section of the anterolateral column and even after bilateral hemisection of the cord at separate levels. This they ascribed to the fact that the ascending visceral pathways run upward within the spinal cord by short fibers with many relays and synapses which have a juxtagriseal position.

The information reported above is based on animal experiments. From recent observations on patients after unilateral anterolateral cordotomy, White *et al.* (1950) have found that distention of the renal pelvis or small intestine is no longer painful on the analgesic side. Furthermore, we have under observation a unilaterally cordotomized patient who has been completely freed of persistent pain after cholecystectomy and multiple operations on the biliary ducts. Only distention of the lower colon, rectum, bladder, and compression of the testicles are still painful after a well-executed transection of the anterolateral quadrants of the cord. Although we cannot be certain that all other visceral pain fibers are concentrated in the spinothalamic tract, it seems reasonably certain that they all ascend in crossed pathways within the anterolateral quadrant.

The vagus nerve, although a conductor of afferent reflex stimuli such as cough reflexes, does not appear to carry pain sensation, except in its superior laryngeal branch and other small rami to the lower trachea and primary bronchi. If it did, abdominal visceral pain would not be abolished by high injuries to the cord or by spinal anesthesia. There are accounts of surgeons injecting the vagi with procaine in the course of cervical sympathectomies without the slightest effect on angina pectoris (Leriche, 1927*B*), and Bradford Cannon (1933) has stimulated the lower vagus in conscious animals by means of buried electrodes without arousing the least sign of discomfort. Grimson, Hesser, and Kitchin (1947) have recently been able to demonstrate that intra-abdominal stimulation of the vagi in man is also painless.* Stimulation of these nerves in conscious patients becomes painful some 3 in. above the diaphragm, but the pain is then referred to the neck.

* Some as yet unpublished observations recently reported to us by Antony Jefferson, F.R.C.S., show that under certain circumstances painful sensation may be aroused by stimulating the abdominal vagi. In the course of subdiaphragmatic vagectomies performed by P. G. McEvedy, F.R.C.S., in Manchester, England, under local anesthesia, the vagi were cut or crushed after the splanchnic nerves had been blocked by injection between the aorta and vena cava against the body of the first lumbar vertebra. Jefferson states that "from seeing some 60 vagotomies I would say that we elicit pain from the posterior vagus in 1 patient out of 4 or 5. Much more rarely we elicit pain from the anterior vagus. It appears usually to be sited in the back at approximately the level of T9 or T10." As Jefferson points out, this unexpected observation may be due to the presence of splanchnic fibers in the vagi which have been missed in the prevertebral block. This possibility could be tested by performing a number of these operations under spinal anesthesia carried as high as the third thoracic level, at which all visceral sympathetic afferents would be blocked.

TABLE II

The Segmental Sensory Innervation of the Viscera

Organ		*Superficial Areas to Which Pain Is Referred*	*Segments at Which Visceral Afferent Axons Enter Spinal Cord* — Thoracic 1	2	3	4	5	6	7	8	9	10	11	12	Lumbar 1	2	Sacral 2	3	4	*Peripheral Visceral Pathway*
Heart		Precordium and inner arm	+	+	+	?														Middle and inferior cervical and thoracic cardiac nerves
Lung		No referred pain *																		
Liver and gall bladder		Right upper quadrant and right scapula						?	+	+	?									Major splanchnic nerve
Stomach		Epigastrium						?	+	+	?									Major splanchnic nerve
Small intestine		Umbilicus									+	+	?							Major splanchnic nerve
Colon	Ascending	Suprapubic											?	+	+					Lumbar chains and preaortic plexus
	sigmoid and rectum	Deep pelvis and anus															+	+	+	Pelvic nerves
Kidney		*Loin and groin*											?	+	+					*Renal plexus via least* splanchnic nerve and upper lumbar rami
Ureter		Loin and groin													+	+				Renal plexus and upper lumbar rami
Bladder	Fundus	Suprapubic																		Lower intercostal nerves
	Bladder neck	Perineum and penis															+	+	+	Pelvic nerves
Uterus	Fundus	Suprapubic region and lower back											+	+	+					Superior hypogastric plexus
	Cervix	Perineum															+	+	+	Pelvic nerves

This table, which differs in only minor respects from the one published by Head (1893), has been compiled from all available experimental and clinical data. More recent evidence, which has necessitated minor modifications of Head's original work, is presented in Chapter III and in the clinical chapters of Part II

* Lung parenchyma is insensitive. Pain from larger bronchi is transmitted over somatic vagal axons. When disease spreads to parietal pleura, pain is transmitted over intercostal nerves

In testing patients before and after various types of sympathetic denervation, he has found no alteration in cutaneous sensory acuity over denervated as compared with undenervated areas of skin. Furthermore, he has been unable to demonstrate any alteration of the sensory threshold after injection of either adrenaline or mecholyl (Chapman and Jones, 1944).

From the data presented above, the role of the thoracolumbar and sacral nerves in the perception of pain may be summarized as follows:

1. Sensory axons which conduct pain to the posterior horn of the spinal cord run with the sympathetic and parasympathetic motor fibers in the visceral nerves. The cervical portion of the vagus and its superior laryngeal branch give off large numbers of somatic sensory fibers to the trachea, larynx, oropharynx, and upper esophagus. Afferent fibers to the bladder, rectum, prostate, and uterine cervix run with the sacral parasympathetic outflow. The sensory innervation of the other thoracic and abdominal organs runs with the thoracolumbar sympathetic system (proved).

2. The small number of viscerosensory receptor endings accounts for the relatively high threshold of visceral sensibility and the poor ability to localize the source of painful stimuli. This arrangement differs in no essential manner from sensory perception in other deep somatic structures such as skeletal muscle (also proved).

3. Misinterpretation of the origin of pain by the central receiving apparatus is an added factor in the poor ability to localize visceral sensation (highly probable).

4. Irritant metabolites produced by axon reflexes may give rise to cutaneous hyperalgesia and muscular tenderness (proof not confirmed).

5. There is no longer any reason to subscribe to Mackenzie's theory of reference of all visceral pain to somatic dermatomes through the mechanism of an irritable focus in the spinal cord.

In this general chapter on the physiology of pain, many special features which apply to the individual organs have not been included. The discussion of these more specific points is reserved for later chapters which deal with the sensory and motor innervation of individual viscera

A final point of interest concerning the role of the sympathetic nerves in pain transmission involves their possible regulation of the sensory threshold of the cerebrospinal system. Scrimger (1936) discussed this interesting subject and pointed out that certain people may train themselves to perceive as pain afferent stimuli from the viscera which do not ordinarily reach the level of consciousness. Continuous or recurring pain may increase its actual perception, so that the sufferer develops all the outward appearance of a confirmed neurotic. It was formerly believed that the autonomic system, which plays such an important role in the emotions, might cause alterations in the sensory threshold. Foerster, with Altenburger and Kroll (1929, and Altenburger and Kroll, 1930), measured the excitability of the somatic sensory nerves by the determination of their chronaxie. These studies showed that stimulation of the sympathetic chains or the injection of adrenaline raises the sensory threshold, a phenomenon which fits in with the well-known diminution of pain sensation in states of anger and fear. On the other hand, following sympathectomy or the administration of choline or pilocarpine (drugs which stimulate the parasympathetic), the threshold of cutaneous sensation is distinctly lowered. Pette (1927) recorded that frequently after sympathectomy there is paresthesia of the corresponding skin area, and Fulton (1928) observed after lumbar ganglionectomy an increase of cutaneous sensation in the leg. Tournay (1921 and 1925) demonstrated similar results in dogs, and mentioned that in 1851 Claude Bernard described hyperesthesia in the skin of the face and ears of rabbits and cats following superior cervical ganglionectomy.

This evidence of changes in sensory threshold could not be measured with certainty until an accurate sensory stimulus was devised. The difficulty was finally overcome by measuring pain thresholds in the skin by thermal radiation (Hardy, Wolff, and Goodell, 1940). This method is simple, rapid, and accurate. The threshold of pain is expressed as the number of small calories which must be applied per second to a square centimeter of skin to produce a distinct sense of pain. This figure appears to be fairly constant in a series of normal subjects. Chapman *et al.* (1947), who have made a study of the sensory threshold at the Massachusetts General Hospital, have found remarkably little variation in the point at which normal controls and neurotic individuals first perceive a painful stimulus, but the *threshold of motor reaction to pain is considerably lower* in the neurotic. While Hardy, Wolff, and Goodell (1940) found that intense pain in any part of the body raised the pain threshold in other parts as much as 35 per cent, Dr. Chapman (1951) has been unable to find any evidence that this is due to the influence of the sympathetic system.

evaporation of sweat from the skin. This is of relatively greater importance at hot than at cold environmental temperatures (Roth *et al.*, 1940). Theoretically, the room walls and objects in the room should have the same temperature as the room air in order to avoid the effects of absorption of radiant energy by the body from the walls and objects in the room, but for clinical purposes it is not necessary to control this. To accomplish rapid cooling of room walls would involve the use of such elaborate machinery for even small rooms that the cost of apparatus and space required for it would be prohibitive except in very special circumstances.

The most useful environmental temperatures for the study of the nervous control of the peripheral circulation lie between 65 and 95° F (19 and 35° C). The air-cooling apparatus should be capable of cooling the room to at least 60° F (15.5° C) in the summer and of warming it to 100° F (38° C) in the winter. Reflex release of vasomotor tone can be accomplished by exposure to a temperature of 82° F (28° C). At this temperature, vasodilatation from the direct effect of heat upon the vessels is unlikely.

Measurement of Skin Temperature. Delicate mercury thermometers are now available (manufactured by L. H. Marks, London, England, and by Rascher and Betzold, Chicago, Ill.) for the direct measurement of skin temperature. While not so accurate or so easily read as some other devices, they can be used for gross estimates of the skin temperature when accurate and extensive mapping is not essential.

The property of certain dissimilar metals to generate an electric current when couplings of them are exposed simultaneously to different temperatures is utilized in the manufacture of extremely sensitive machines for the measurement of skin temperature. Such instruments are available with a single exploring junction or thermocouple, which can be moved manually to plot the surface temperature at desired points on the skin. Apparatus is also made with multiple (eight or twelve) junctions which are attached to the skin at selected points and record automatically in rotation. Excellent equipment for these purposes is manufactured by the Leeds and Northrup Co. of Philadelphia, Pa., and by Minneapolis-Honeywell of Minneapolis, Minn.

Skin-color Chart. Changes in the color of the skin are determined primarily by changes in the blood within the capillaries and venules of the papillary layer of the skin. The color of the skin, then, is an important physical sign in peripheral vascular disease. Dramatic changes in the color of the skin (hands, feet, face, nose, ears) can be produced by exposure to cold and by procaine block of the sympathetic nerves para-

CHAPTER VII

Methods of Study

The principal function of the sympathetic nervous system in the periphery is the control of arteriolar tone which, in turn, modulates the quantity of blood flowing through the skin. In a cool environment the temperature of the skin is conditioned, for the most part, by the volume of blood which flows through the skin per unit of time. Changes in the skin temperature can be used, therefore, for studying the activity of the sympathetic nerves when intact and when interrupted chemically or surgically.

A second function of the peripheral sympathetic system is its control of sudomotor activity. This affords a second general method for studying the activity of this component of the nervous system, namely, the measurement of sweating on the surface of the skin.

In order to study these autonomic functions, the basic requirement is a room in which the temperature can be controlled within narrow limits. It must be free of drafts and the temperature must be uniform throughout it. The room should be large enough to permit such procedures as the administration of spinal anesthesia and procaine block of peripheral nerves and of the paravertebral sympathetic chains.

Changes in color, temperature, and moisture of the skin can be detected by inspection and by the unaided hand for gross approximations. The recording of accurate objective data, however, requires the use of instruments which will be described in this chapter.

I. Techniques and Instruments

Constant-temperature Room. Since even slight changes in the environmental temperature are recorded directly by the thermocouples and plethysmographs and through the effects upon the circulation of the skin, it is essential that the air-conditioning apparatus be capable of maintaining constancy in the environmental temperature. Insensitive thermostats and overloading of the apparatus may produce "cycling" of sufficient magnitude to vitiate the tests performed. Baffles or perforated ceilings are used to avoid drafts from the air let into the room. It is well to have some control over the humidity of the room because of the cooling effect of

the conjunctiva (Knisely *et al.,* 1947). Photographic attachments to the microscope permit photomicrography (Fig. 44) and cinematography (cf. Knisely *et al.,* 1945 and 1947).

Reflex Vasodilatation. The ability of the peripheral blood vessels to dilate and thereby increase the rate of blood flow through them can be measured by inducing vasodilatation reflexly. The physiologic stimulus for this is exposure of the body to external heat. The increased temperature so imparted to the blood returning from the skin inhibits the activity of the vasomotor center in the medulla, and thereby approximates a paralysis of sympathetic activity in the periphery. The resulting release of the arterioles from sympathetic control can be measured by the effect upon the skin temperature, rate of blood flow, and volume of the pulse wave.

In estimating the degree of reflex vasodilatation it is essential to note the position of the subject. The blood flow in the extremities is aided by the dependent position (Scheinberg *et al.,* 1948). The volume of the pulse wave is improved, within limits, by elevation (Goetz, 1950). When the degree of arteriolar dilatation is measured by its effect upon the pulse wave or the rate of blood flow, it is not necessary to warm the subject apart from the room. The entire room may be heated, but when the desired temperature is reached it should be held constant for the necessary period of equilibration. We have come to employ a temperature of 85° F (30.5° C) for one hour.

Syringes and Needles for Injection Tests. As described in Chapter XX, procaine, alcohol, or phenol are injected into sympathetic structures for testing the role of the sympathetic in vasomotor activity or for therapeutic purposes. Appropriate needles and syringes are essential to accomplish these purposes. For blocking sympathetic fibers in peripheral nerves (posterior tibial, ulnar, median, peroneal) small-bore needles (22 to 24 gauge) 2 to 5 cm in length are very satisfactory. Somewhat longer needles, depending upon the size of the subject, are necessary for injecting the sciatic nerve. For reaching the paravertebral ganglia or the celiac ganglion, needles 10 cm in length should be used. Shorter needles cannot be counted upon to reach the paravertebral ganglia even in the average-sized individual. As a general surgical principle, the caliber of the needle used should be the smallest consistent with the work expected of it. For reaching the sympathetic trunk, the needle should be of sufficient caliber to afford a certain degree of stiffness to aid the operator in directing its course. The Labat type of syringe and needles, of the necessary length and 0.9 mm in diameter, are excellent for this purpose and are manufactured by the Anglo-French Drug Co. of New York. The use of segments of fine rubber tubing

vertebrally or peripherally. In order to standardize these color changes and to permit their accurate objective recording, Sir Thomas Lewis (1929*A*) prepared a color chart depicting the several possible skin colors and identifying them by letter and number. The chart can be duplicated in other laboratories and is a useful adjunct to the laboratory equipment for studying the peripheral circulation.

Oscillometer. It is often useful to have some quantitative estimate of the degree of pulsation in the large arteries of the extremities when pulses in them are not palpable or are greatly diminished. Instruments are available for measuring and for recording these pulsations. The oscillometer devised by Pachon and manufactured by Boulitte in Paris is really a plethysmograph. The expansile pulsations of the part of the limb encircled by the inflatable cuff are transmitted as pressure waves into a sensitive capsule connected to a needle and scale in arbitrary units. A popular oscillometer is that manufactured by U M.A. Inc. of New York City as the Collens Sphygmo-oscillometer. Self-recording oscillometers are manufactured by the Taylor Instrument Companies of Rochester, N. Y., and by the Cameron Heartometer Co. of Chicago, Ill. Basically, the same information can be obtained by observing the oscillations of the mercury column in the ordinary sphygmomanometer used in measuring the blood pressure. The oscillometers described above avoid the inertia of a mercury column and enlarge the scale for convenience of reading. A drawback common to the oscillometers available at present is that the units of measurement are arbitrary and are not comparable among the various instruments. An apparatus which can be used both as oscillometer and as plethysmograph and which can be read in units of either volume or pressure is manufactured by the Grass Instrument Co. of Quincy, Mass

Capillary Microscopy. The number of capillaries per unit area of skin, their configuration, and the speed of blood flow through them can be studied by means of capillary microscopy. An ordinary monocular or preferably a binocular microscope affording 50 to 100 times magnification can be used. Illumination is obtained by incident light reaching the area under study at an angle of 45 deg and filtered through a flask of clear blue solution The surface examined is covered with a drop of cedar oil. It is essential that a minimum of manipulation of the skin be done if capillaries in their natural state are to be studied Excessive irritation by scrubbing, heat, or chemicals is to be avoided unless these variables are the subject of study. The most convenient surface for this purpose is the nail bed at its junction with the cuticle, though other areas have been studied as well, such as the skin (Bordley *et al.*, 1938) and

By recording through a photoelectric cell with very little amplification the amount of light passing through the digit from a constant light source, it is possible to measure changes in volume of the digit by the degree to which it impedes the passage of light through it. By using standard filters for calibration, Hertzman (1938) and Hertzman and Dillon (1940) adapted this technique to the study of the digital circulation in man.

The Thermostromuhr. The principle of the Hill and of the Rein thermostromuhrs has been adapted by several different investigators to the study of the rate of blood flow in arteries (Hill, 1920; H. Rein, 1928; Baldes and Herrick, 1937; Linton *et al.*, 1941; Bennett *et al.*, 1944). Fundamentally, these instruments depend upon the cooling effect of the flowing blood upon a heated terminal within the arterial lumen or upon the heat imparted to blood flowing past a segment of artery which is heated externally by means of appropriate electrodes. While much useful data have been obtained with regard to factors influencing the rate of blood flow by this method, the pitfalls inherent in it are so numerous that the results of such studies must be accepted with caution (Gregg *et al.*, 1942; Bennett *et al.*, 1944). Montgomery (1929 and 1932) has used a modification of the Ludwig stromuhr for similar studies.

Radioactive Substances. The popularity of radioactive substances as "tracers" in medical investigation has extended to the field of research in problems of the peripheral circulation. For the study of effective circulation in the periphery radioactive sodium has been used. B. C. Smith and Quimby (1945 and 1947) studied the time course of its build-up in the extremities after intravenous injection, and Kety (1948 and 1949), followed by Elkin *et al.*, (1948), P. W. Stone and Miller (1949), Murphy *et al.* (1950), and Boatman *et al.* (1950), studied its clearance rate when injected into the tissues. While there is obvious merit in exploring these methods for dealing with problems of the peripheral circulation, the results must be interpreted with caution. The behavior of a fully diffusable ion like sodium in the circulation and in the tissues is conditioned by so many factors other than the rate of blood flow that reliable data must await the development of radioactive substances with physical properties which limit their freedom of crossing membrane barriers.

Tissue Oxygen Tension. The use of minute platinum electrodes inserted into tissue and balanced against a standard calomel cell has been described by Davies and Brink (1942) for measuring the oxidation potential and thereby the pO_2 in tissues. Little use has been made of this technique for the study of the peripheral circulation in disease, but with

and a sterilizable millimeter rule for marking the depth to which the needle is to be introduced is described in Chapter XX.

Determination of Skin Calorimetry. The amount of heat delivered by the skin to its environment per unit of time can be measured accurately by calorimetry and can serve as a useful index of the circulation to the part studied (Stewart, 1911; Kegerreis, 1926). As Sheard (1927) has pointed out, the actual transfer of heat from the skin to its environment depends upon a number of different variable factors, such as the conductivity of the skin and the number of capillaries in the skin per unit of surface area. Accurate standards, especially for the transfer of data from one subject to another, are therefore impossible to establish. The technique could be useful for recording quantitatively changes in the circulation in the same individual. It is cumbersome, however, and comparable information can be obtained by simpler methods.

Plethysmography. The plethysmograph is an instrument for recording changes in the volume of a part under examination. The technique for using it to measure the rate of blood flow in an extremity was described first by Hewlett and van Zwaluwenburg in 1909. Since that time various modifications of the instrument have been described. Freeman (1935) applied the technique to studies of the blood flow in the hand, and Stead and Kunkel (1938) described an adaptation of the method for the foot. It can be used for studies of the blood flow in the forearm or leg, with physiologic exclusion of the hand and foot, so that the tissue mass is largely muscle (Grant and Pearson, 1938; Abramson and Ferris, 1940). The rate with which the extremity swells when the drainage of blood through the veins is obstructed by a cuff is taken to represent the rate at which blood is entering the limb. Some of the important points to be observed for obtaining useful plethysmographic records have been described by Abramson *et al.* (1939), and a critique of plethysmographic methods was presented by Landowne and Katz in 1942.

The same principle of plethysmography has been applied to studies of volume changes in the digits (C. A. Johnson, 1932 and 1940; Goetz, 1935; Turner, 1937; Wilkins *et al.*, 1938; Burton, 1939; Burch, 1947). Measurements of blood flow in the digits have been made by means of the digital plethysmograph (Wilkins *et al.*, 1938; Burton, 1939; Johnson, 1940; Goetz, 1943, 1948.4, and 1950; Robertson *et al.*, 1949). An extremely sensitive direct ink-writing plethysmograph has been described recently by Simeone, Cranley, Grass, Lynn, and Linton (1952). It can be used as an oscillometer to record and measure the pulsations at any desired level of the extremity as well as for a digital plethysmograph

drug is therefore contraindicated for cerebral angiography in elderly patients in whom the cerebral circulation is already critical. Cases have been reported in which thrombosis and gangrene were thought to have been precipitated by the injection of Diodrast for arteriography in the extremities, and recently fatal mesenteric thrombosis has been reported to follow attempted aortography with sodium iodide (Wagner and Price, 1950). If sensitivity to Diodrast is ruled out, however, and if care is taken to inject the drug into the arterial lumen, the dangers of this method of arteriography are minimal.

Thorotrast, a colloidal solution of radioactive thorium dioxide, possesses none of the irritant qualities of iodine compounds. E. V. Allen and Camp (1932) used it for arteriography and, by injecting 10 to 25 cc of the drug, obtained excellent visualization of the arteries without pain, spasm, or irritation. As a rule, 12 to 20 cc is sufficient to permit visualization of the arteries of the lower extremity and 5 to 10 cc for those of the upper extremity. These volumes do not introduce an injurious amount of radioactivity into the body. While not irritating when injected within the arteries or veins, Thorotrast induces an extensive fibrosis when introduced outside the blood vessels, and sarcomatous degeneration has been reported as the result of this extravascular reaction. When Thorotrast is used, it is preferable to expose the artery to be examined by means of a small incision to be absolutely certain that none of the solution is allowed to extravasate.

The technique of arteriography has been described in detail by Veal and McFetridge (1934, 1935, and 1936) and by Allen and Camp (1935). An excellent review of the subject has been written by Shumacker and Godley (1948). In cerebral arteriography the risk of hemiplegia after the injection of Diodrast is a serious one, even in the absence of demonstrable sensitivity. The complication has been encountered several times, usually transiently, at the Massachusetts General Hospital, and at present Diodrast is used only in young individuals without evidence of vascular disease. In older patients with signs of obliterative vascular disease, Thorotrast is used for cerebral angiography. In the extremities Diodrast has been used as a rule for arteriography. Fifteen to 30 cc of 35 to 70 * per cent Diodrast are injected with 2 cc of a 1 per cent solution of procaine added to it. With this mixture pain is felt only if the needle happens to slip out of the artery and some of the solution is injected into the tissues around it. Otherwise, a sensation of warmth, varying from a mild degree to intense unpleasant heat, is felt in the extremity by the subject. Later, the feeling of warmth is generalized. We have seen no gross evidence of

* Seventy per cent Diodrast should never be used in cerebral angiography.

further developments the method will undoubtedly provide important data.

Arteriography. Visualization of the caliber and configuration of the arteries is a useful aid in the evaluation of the status of the peripheral circulation. It is true that in most cases a satisfactory appraisal can be made on the basis of the physical examination alone. An arteriogram, nevertheless, can yield information on detail not obtainable by other means. It permits localization of the origin or origins of aneurysms and demonstrates their type and extent. The exact localization and characteristics of an arteriovenous aneurysm or fistula can be defined. In the case of chronic arteriosclerotic aneurysms in critical locations, such as those of the popliteal artery, an arteriogram can demonstrate the characteristics of the collateral vessels upon which will depend the arterial blood supply to the leg and foot if the aneurysm is resected. Arteriograms are indispensable if one is to practice segmental arteriectomy with or without vein graft (Leriche, 1946; Holden, 1950), or if removal of the atheromatous obstruction to blood flow is to be done, as practiced by dos Santos (1949).

The technique of arteriography is not easy and requires time and experience for mastery. A solution which obstructs the passage of X rays through tissues must be injected into the lumen of a major artery. A variety of solutions have been used for this purpose, including Thorotrast and a number of preparations of iodine. Sodium iodide, an excellent contrast medium, proved too irritating and toxic. Iodized oil has been used by Saito *et al.* (1930), who obtained excellent roentgenographs without complications. The fear of oil embolism, however, has prevented the general use of oil preparations. Methiodol (sodium monoiodomethane sulfonate) was used by Pearse and Warren (1931) without untoward incident. They used 25 cc of a 40 per cent solution, injecting it through a 20-gauge needle passing obliquely through the wall of the femoral artery. In their technique they exposed the femoral artery under local anesthesia. Others have not found this necessary except under special circumstances. At the present time Diodrast (a diethanolamine salt of 3,5-diiodo-4-pyridone-N-acetic acid) is the most popular of the iodine-containing preparations used in arteriography. Occasional serious systemic reactions have resulted from the use of this substance in intravenous pyelography, and it is essential to test the subject for sensitivity to the drug before it is administered. It does not produce arterial spasm, but there is some evidence that Diodrast is irritating to capillaries and the tissues which surround them (Broman and Olsson, 1948 and 1949). Temporary spasm may occur in capillaries and arterioles following the injection of Diodrast, and this

drug is therefore contraindicated for cerebral angiography in elderly patients in whom the cerebral circulation is already critical. Cases have been reported in which thrombosis and gangrene were thought to have been precipitated by the injection of Diodrast for arteriography in the extremities, and recently fatal mesenteric thrombosis has been reported to follow attempted aortography with sodium iodide (Wagner and Price, 1950). If sensitivity to Diodrast is ruled out, however, and if care is taken to inject the drug into the arterial lumen, the dangers of this method of arteriography are minimal.

Thorotrast, a colloidal solution of radioactive thorium dioxide, possesses none of the irritant qualities of iodine compounds. E. V. Allen and Camp (1932) used it for arteriography and, by injecting 10 to 25 cc of the drug, obtained excellent visualization of the arteries without pain, spasm, or irritation. As a rule, 12 to 20 cc is sufficient to permit visualization of the arteries of the lower extremity and 5 to 10 cc for those of the upper extremity. These volumes do not introduce an injurious amount of radioactivity into the body. While not irritating when injected within the arteries or veins, Thorotrast induces an extensive fibrosis when introduced outside the blood vessels, and sarcomatous degeneration has been reported as the result of this extravascular reaction. When Thorotrast is used, it is preferable to expose the artery to be examined by means of a small incision to be absolutely certain that none of the solution is allowed to extravasate.

The technique of arteriography has been described in detail by Veal and McFetridge (1934, 1935, and 1936) and by Allen and Camp (1935). An excellent review of the subject has been written by Shumacker and Godley (1948). In cerebral arteriography the risk of hemiplegia after the injection of Diodrast is a serious one, even in the absence of demonstrable sensitivity. The complication has been encountered several times, usually transiently, at the Massachusetts General Hospital, and at present Diodrast is used only in young individuals without evidence of vascular disease. In older patients with signs of obliterative vascular disease, Thorotrast is used for cerebral angiography. In the extremities Diodrast has been used as a rule for arteriography. Fifteen to 30 cc of 35 to 70 * per cent Diodrast are injected with 2 cc of a 1 per cent solution of procaine added to it. With this mixture pain is felt only if the needle happens to slip out of the artery and some of the solution is injected into the tissues around it. Otherwise, a sensation of warmth, varying from a mild degree to intense unpleasant heat, is felt in the extremity by the subject. Later, the feeling of warmth is generalized. We have seen no gross evidence of

* Seventy per cent Diodrast should never be used in cerebral angiography.

vascular spasm following peripheral injection. Indeed, a pink flush has been observed in the skin distal to the point of injection.

As already stated, the value of arteriography lies in special situations in diseases of the peripheral circulation. Other than for purposes of demonstrating the effects that sympathectomy may have had on the circulation after operation, arteriography has no practical value for studying the relationship between the sympathetic nervous system and the circulation in patients with peripheral vascular disease. Recently, Leriche pointed out to us, however, that arteriograms may be very useful for selecting patients with arteriosclerotic disease in the extremities for sympathectomy. In his experience the best results are obtained in patients in whom the atheromatous process within a major artery is localized to a segment of the artery rather than spread diffusely throughout the arterial trunk.

II. *Preoperative Tests*

A. VASOMOTOR SYSTEM AND SKIN TEMPERATURE

Proper evaluation of skin-temperature data necessitates their interpretation in relation to certain well-known features of the vasomotor system and the control of skin temperature. Talbot (1931) has published an extensive study of the skin temperatures of children, pointing out the influences of varying external and internal conditions upon them. In order to obtain comparable results at different times in the same patient or to compare data obtained in different laboratories, it is essential that the studies be done in a room with rigidly controlled temperature and humidity. Ideally, a period of sixty minutes should be allowed for the subject to become stabilized at the cold or hot temperatures. Observations should be made at the same time of day and under basal conditions in any given study in order that observed changes may represent real effects and not merely diurnal variations in the peripheral circulation, as described by Simpson (1931). On very hot days, in the presence of fever, or with cachexia of advanced malignant disease, peripheral vasoconstriction in response to cold is abnormally sluggish, and data obtained under these circumstances are of questionable value.

There is very little variation in the skin at symmetrical points on the right and left sides of the body. The variation is seldom more than 1.8° F (1° C). Physiological studies can therefore be made on the blood vessels of one extremity denervated surgically or by procaine block using the other side as control. Referring to Figure 30, in each of these charts curves are represented illustrating the average comparative temperatures com-

monly observed at different levels on the limbs at a room temperature of 68° F (20° C). These include the gradients in typical normal and in vasospastic extremities, as well as those after sympathectomy.

There is normally a gradient in the skin temperature, falling as the periphery of the body is reached. The coolest points are on the fingers and toes. The hands and the feet show somewhat less cooling, and a steep gradient is formed until the knees and elbows are reached when the gradient with the trunk and head becomes almost nonexistent (Fig. 30). The

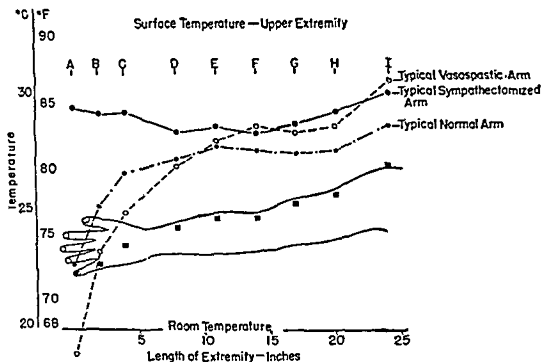


Fig. 30. A. Surface-temperature gradients in the upper extremity before and after sympathectomy for relief of vasospasm.

The typical surface-temperature curve in a patient with Raynaud's phenomenon owing to increased sympathetic activity is illustrated before and after sympathectomy. A typical normal curve is inserted for comparison.

gradient in the periphery is most easily shown in a subject who is undergoing tests for the first time or in an apprehensive individual. The emotional reaction is sufficient to excite a reflex vasoconstriction which is normally maximal in the hands, feet, fingers, and toes, thereby exaggerating the gradient. The explanation for the gradient is that vasoconstrictor tone is maximal in the hands and feet, which have among their many functions the control of heat loss from the body into the environment. The relatively large surface area per unit mass in these organs makes them especially suited to this function in man. The gradient is abolished when the occasion arises for losing heat from the body, such as with increased metabolism;

upon exposure to a hot environment; when the hypothalamic vasoconstrictor outflow is reduced as in sleep or after certain drugs (barbiturates, alcohol, ether); and when vasoconstrictor impulses are blocked from reaching the periphery by sympathectomy or procaine block.

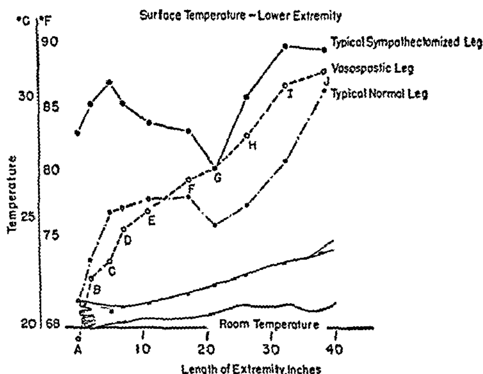


Fig. 30. B. Surface-temperature gradients in the lower extremity before and after sympathectomy for relief of vasospasm.

There is less variation between the surface-temperature curves of normal and vasospastic legs than is the case with upper extremities. This is because there is greater sympathetic tone in the normal lower extremity. After complete sympathectomy the rise in surface temperature is largely confined to the distal third of the leg.

We have found it useful to make peripheral surface-temperature charts of each patient after exposure for one hour to a room temperature of 68° F (20° C) with the trunk lightly covered in a standard manner and the extremities exposed to the room temperature.

The average maximal vasodilator response when vasoconstrictor tone is abolished was designated by Morton and Scott (1930) as "the normal vasodilatation level." In our experience, early after sympathectomy, during spinal anesthesia, or during procaine block of the paravertebral ganglia or peripheral nerves, the resulting vasodilatation maintains the skin temperature of the digits at about 93° F (33.5° C) in an environmental temperature of 68° F (20° C). Later after sympathectomy the digital skin temperature may be as low as 90° F (32° C). Failure to attain these tem-

peratures suggests incomplete interruption of vasoconstrictor tone or obliterative disease of the blood vessels.

In estimating the significance of the quantitative rise in skin temperature after a diagnostic procaine nerve block, it is important to appreciate that the significant feature of the rise in temperature of the skin of a given digit is not the absolute rise, but how nearly the rise approaches the normal vasodilatation level. The absolute rise depends in part upon the initial coolness of the extremity, while the degree to which the skin temperature approaches the normal vasodilatation level is a measure of the degree or completeness of arteriolar dilatation. If the maximum surface temperature recorded in a given patient is subtracted from the normal vasodilatation level, an index of the amount or the degree of organic arterial occlusion is obtained (Fig. 31). In the typical early case of Raynaud's disease the skin temperature reaches the normal vasodilatation level when the vasoconstrictor influences are interrupted, but if the disease is advanced and sclerodermatous changes have produced a constricting fibrosis about the digital arterioles, the resulting vasodilatation may fall far short of the normal level. The advanced arteriosclerotic patient cannot be expected to show any appreciable elevation in peripheral temperature, but many early cases of thromboangiitis obliterans respond with a striking degree of vasodilatation when the tests are applied.

It is important to note that even patients with fairly severe arteriosclerosis will approach the normal level of vasodilatation if one waits long enough (i e., up to three hours). It is important, therefore, to set a time limit for taking the skin-temperature readings following a diagnostic procedure. We have found a period of one hour after spinal anesthesia, procaine block, or reflex vasodilatation to be satisfactory.

B. TECHNIQUES FOR DISTINGUISHING VASCULAR SPASM FROM ORGANIC VASCULAR OCCLUSION

All of the tests employed depend basically upon the arteriolar dilatation which normally follows the release of vasoconstrictor tone and its effect upon the skin temperature, the pulse volume, and the rate of blood flow. In the previous editions of this book, one of the methods described in detail was that of injecting foreign protein intravenously and studying the vascular responses during the reaction (A. W. Allen and Smithwick, 1928). This procedure was first described by G. E. Brown in 1926 (*A*) as a means of distinguishing between vasospasm of nervous origin (Raynaud's disease) and organic occlusion of the arteries (arteriosclerosis and thromboangiitis obliterans). It was subsequently developed as a thera-

peutic agent for thromboangiitis obliterans. This test, which has not been used by us during the past ten years, since better information can be obtained by less cumbersome and less dangerous means, will not be described in this edition.

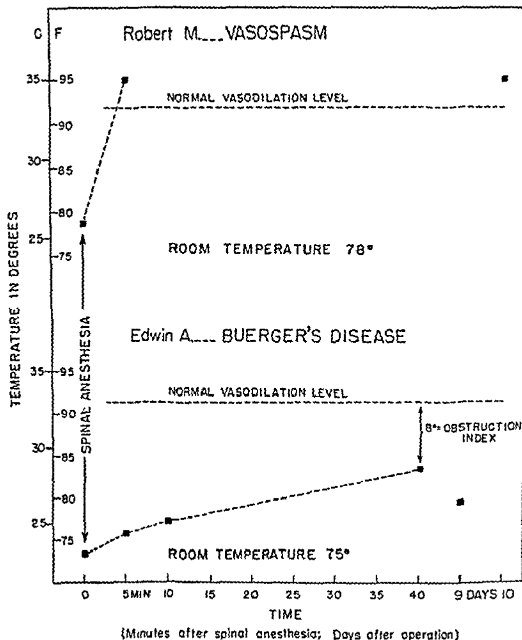


Fig. 31. Spinal-anesthesia test.

The upper chart shows the surface-temperature response in the toes in a case of uncomplicated vasospasm. The second patient, with organic arterial occlusion from thromboangiitis obliterans, has an additional vasospastic handicap. Ganglionectomy, performed on the indication of this test, was followed by healing of a sluggish toe amputation stump and by a lasting increase of circulation in the foot.

At the present time three general procedures are used in the Peripheral Vascular Laboratory of the Massachusetts General Hospital for testing the ability of the blood vessels of the extremities to dilate when released from sympathetic control:

Diagnostic Procaine Block. In 1930 (*A* and *B*) White reported that sympathetic vasomotor fibers could be blocked temporarily by procaine nearly as effectively as by actual operative methods. These articles showed that vasodilatation approaching the maximal can be accomplished by paralyzing the sympathetic fibers in the anterior roots (spinal anesthesia), by infiltrating procaine around the sympathetic ganglia and their communicant rami (paravertebral block), or by infiltration of the postganglionic axons in the mixed spinal nerves (peripheral nerve block). A few weeks preceding the publication of this paper Brill and Lawrence (1930) reported the use of spinal anesthesia for this purpose, and shortly thereafter Morton and Scott (1930) published further studies showing the value of spinal block for such measurements in the lower extremity. Later, they advocated blocking the peripheral nerves (posterior tibial, ulnar, or median) as the simplest method of estimating the vasodilator response. Sir Thomas Lewis (1929*B*) had previously utilized ulnar nerve block at the elbow to study the rise of temperature in the little finger. All of these methods temporarily paralyze the vasomotor impulses and give a quantitative measure of the elevation in peripheral temperature which can be expected to follow sympathectomy. Figure 32 illustrates the expected rise in skin temperature in the normal hand and foot, respectively, after blocking the peripheral nerves.

The various forms of sympathetic paralysis with procaine are useful indices of the degree of vasodilatation which may be expected to result from sympathectomy. The acquisition of a certain degree of spontaneous tone by the smooth muscle of the arterioles usually diminishes somewhat the initial dilatation seen immediately after sympathectomy or procaine block. The extent to which tone is resumed spontaneously by the arterioles cannot be foretold by any of the tests available. Its mechanism is obscure (Cannon, 1937).

Nerve block with procaine is the most informative of the procedures commonly employed to test the degree of control which the vasomotor center exerts on the peripheral circulation. Peripheral nerve block and even injection of the paravertebral ganglia cause less discomfort and are less risky than the reaction produced by the administration of typhoid vaccine intravenously. One or other of these forms of chemical blocking of the vasoconstrictor impulses is generally considered the most useful

Fig. 32. Rise in skin temperature of normal subject following peripheral nerve block with 1 per cent procaine.

A. Right fifth finger after ulnar and median nerve block

B. Right great toe after posterior tibial nerve block

test to aid in the selection of patients with Raynaud's disease and Buerger's disease for sympathectomy. When the distal arteries are partially occluded and the peripheral blood flow depends largely on collateral circulation, a paravertebral block of the sympathetic chain is likely to give a more accurate measure of the possible effect of sympathectomy than the injection of a peripheral nerve.*

The technique of performing these injections is very well described in Labat's textbook (1930) and also in articles by White (1930*A* and *B*), Morton and Scott (1930 and 1931), Flothow (1931), and de Takats (1931). A revised monograph of techniques for infiltrating the sympathetic nerves and ganglia has been published recently by Tosatti (1947). In performing diagnostic spinal block, it is best to have the patient lie on his side and to inject slowly into the fourth lumbar interspace 100 mg of procaine crystals dissolved in 3 cc of spinal fluid. A typical response to this injection in a case of Raynaud's disease is shown in Figure 31. The lower curve illustrates the slower and less-striking response obtained in a patient with thromboangiitis obliterans who showed a definite degree of vasoconstrictor spasm, and was later subjected to lumbar ganglionectomy as a result of this test. A dilute solution of procaine (0.2 per cent) can selectively block the autonomic fibers of the spinal roots within the dura and can thereby release the peripheral vessels as well as the viscera from control by the autonomic nerves throughout the area reached by the solution. The somatic motor and most of the somatic sensory fibers except those conducting pain are left intact. The technique for using this test for studying the autonomic control of the circulation has been published by Sarnoff and Arrowood (1946).

In carrying out paravertebral injection of the stellate ganglion, 5 cc of 1.0 per cent procaine-adrenaline is injected against the sides of the seventh cervical or first thoracic vertebrae. The technique of this procedure is described on page 467 (Fig. 100). Procaine injected in this region will diffuse freely, infiltrating the ganglionated chain and the communicant sympathetic rami to the brachial plexus. Blocking these structures results in Horner's sign, cessation of perspiration, and vasodilatation in the arm and corresponding side of the face (Fig. 33).

Following infiltration of any peripheral nerve with procaine, there results a vasomotor paralysis over the area of anesthetized skin. For testing the vascular responses in the foot to release of vasomotor control, the

* Procaine block of a single peripheral nerve does not always give a maximal vasodilatation in its sensory area. A greater degree of vasodilatation is obtained in the ulnar area of the hand, for instance, when both ulnar and median nerves are blocked than when the ulnar nerve alone is blocked.

simplest method is to inject the posterior tibial nerve at the internal malleolus (Fig. 34) (Morton and Scott, 1931). In the hand, vasodilatation can be easily produced for the fifth finger by blocking the ulnar nerve at the elbow (Lewis, 1929*B*), at the wrist, or in both places. In some instances

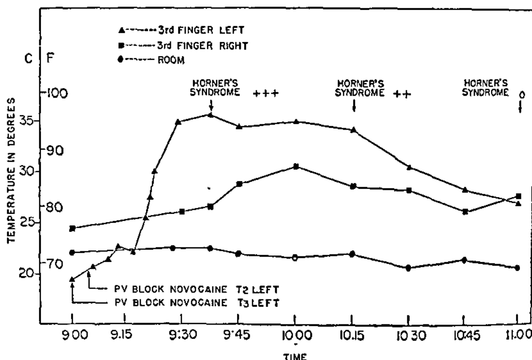


Fig. 33. Results of paravertebral procaine injection in a patient with uncomplicated vasospasm.

of severe Raynaud's disease or Raynaud's phenomenon, complete vasodilatation or inhibition of vasoconstriction in the little finger does not result from blocking the ulnar nerve alone but is obtained when both ulnar and median nerves are blocked. In both the hand and the foot, a complete block of vasomotor impulses cannot be depended upon unless paresthesia is produced by the needle before procaine is injected.

General Anesthesia. Most general anesthetics cause vasodilatation throughout the entire cutaneous area comparable to the regional effect of procaine block of the sympathetic ganglia or the mixed peripheral nerves. W. J. M. Scott and Morton (1930) described this phenomenon under anesthesia with ether, nitrous oxide–oxygen, and tribromethyl alcohol. Vasodilatation in the skin is also produced by anesthesia with the barbiturates. Alcohol, even in amounts well below the anesthetic level, is known to be an excellent vasodilator for certain areas of the body (see Chap. V). Under the influence of these agents the mechanism for the

conservation of body heat is lost, and the temperature of the blood slowly falls.

Figure 35 shows the variation in skin temperature during induction, full surgical anesthesia, and recovery from ether anesthesia. The vaso-

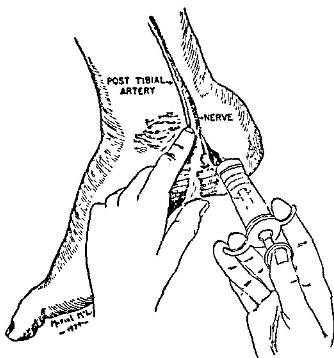


Fig. 34. Posterior tibial nerve block behind internal malleolus.

constrictor gradient is abolished as soon as a depth of anesthesia is reached which produces moderate muscular relaxation. Under gas–oxygen there is an actual vasoconstriction during the period of struggle, so that in some cases ether may have to be added to induce an adequate paralysis of vasomotor as well as striated muscle tone.

Observations under general anesthesia are obviously important for studying the behavior of the vasomotor system under such conditions, but they are seldom indicated as a technique for testing the degree of vasomotor control of the peripheral circulation in individual patients. Other methods are easier for both investigator and subject.

Peripheral Vasodilatation by External Heating. Pickering (1932) has shown that when the temperature of the blood is elevated as little as from 0.018 to 0.072° F (0.01 to 0.04° C) vasodilatation occurs in the skin through the action of the central heat-regulating mechanism. A number of very simple and useful tests based on this fundamental principle have been

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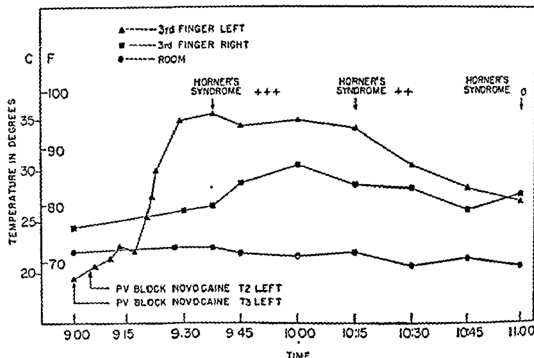


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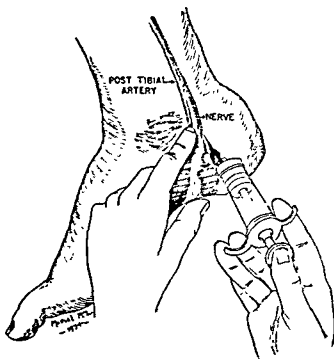


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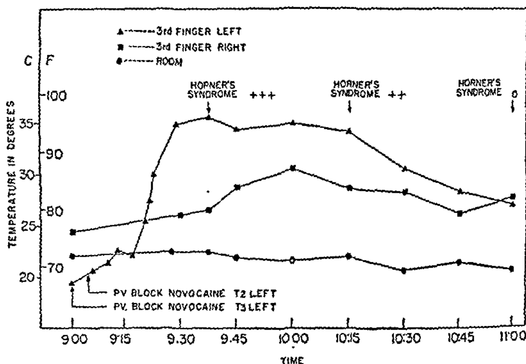


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when the hands are to be tested. In patients with vasospasm, dilatation of the vessels in the skin begins in fifteen minutes and should be complete within a half hour. In patients with occlusive disease of the blood vessels, however, the onset of vasodilatation is not nearly so prompt nor does it usually reach its maximum within the half hour. This may require as long as two hours or more, longer than is safe to heat such extremities. One of our patients with organic peripheral vascular disease developed a second-degree burn of the feet after immersion for one hour at 105° F (40° C).

While these methods may have their drawbacks, they are extremely simple and necessitate no expensive apparatus other than the thermoelectric thermometer, which is indispensable to any clinic undertaking sympathetic surgery for vascular diseases. Whichever method appeals most to the individual surgeon and fits best with available space and equipment is the one that should be adopted and used routinely so as to gain maximum familiarity with the techniques involved. It should be realized, however, that at times the response is not clean cut. Whenever there is the least uncertainty, the patient should be tested again by the alternative method described in the following section.

Alternative Method Employed at Massachusetts Memorial Hospitals. Instead of inducing vasodilatation, an alternate method of study has been developed by one of us (R. H. S.) which appears to be very helpful in the selection of cases for extremity sympathectomy. This depends upon the temporary induction of vasoconstriction as a means of evaluating the magnitude of the vasomotor component.

If the extremities are exposed to a warm environment (83° F; 28° C) for one hour and on another occasion to a cool environment 68° F; 20° C) for a similar period, the trunk being covered by a sheet and a thin cotton blanket, the difference in the temperatures of the tips of the digits in the two environments serves as a measure of the activity of the vasoconstrictor mechanism. The warm-room digital temperatures have been divided into three zones. In zone 1, the digital temperature is below room temperature (83° F; 28° C); in zone 2 it ranges from 83 to 87° F (28 to 30° C) inclusive; in zone 3 it is 88° F (31° C) or more. The cold-room digital temperatures have been divided into four zones. In zone A digital temperature is below room temperature (68° F; 20° C); in zone B it ranges from 68 to 74° F (20 to 23° C) inclusive; in zone C from 75 to 79° F (23.5 to 26° C); and in zone D it is 80° F (26.5° C) or higher. By combining the warm- and cool-room digital temperature zones, there are twelve categories into which a particular extremity may fall. The most vasospastic category is 1A, the digital temperatures being below room temperature

developed for the differentiation of vasospasm from arterial obliterative disease.

Lewis and Pickering (1931) described a cabinet in which the patient's body could be subjected to an environmental temperature of 125° F

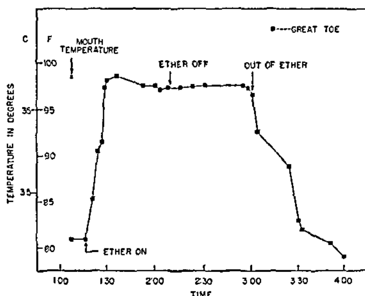


Fig. 35. Vasodilatation under ether anesthesia.

(51° C) while the head and arms were exposed to the cooler room temperature (68° F; 20° C). As soon as the body within the heated cabinet begins to perspire, the individual with normal circulation responds by a rapid warming of the hands to the normal vasodilatation level. The apparatus can be adapted to measurements on the feet as well as on the hands We have used a heating cabinet, essentially a cradle heated by incandescent electric light bulbs arranged so as to avoid burning the subject, with which the trunk may be heated, leaving the arms and legs exposed to the room temperature for testing. While the apparatus has worked fairly well for most, though not all, individuals with normal circulation, it has not been nearly so efficient as nerve block for patients with even mild degrees of arterial occlusion. A similar experience with these methods of applying external heat has been reported by Uprus *et al.* (1936). Goetz (1950), however, finds the technique suitable for his purposes and uses it routinely.

Gibbon and Landis (1932) utilized this same principle of applying external heat by having the patient sit with forearms immersed in hot water (110 to 112° F; 43 to 45° C) while the lower extremities to be tested are exposed to the cool atmosphere of the room, or by immersing the legs

By studying each extremity in this fashion, it is possible to place it in one of the twelve categories. This has so far been done for 185 upper and lower extremities having either vasomotor or obliterative disease prior to operation and again in the early postoperative period before regeneration could be a factor. It was decided that if, after sympathectomy, the digital temperatures were 8° F (4.4° C) or more higher than before operation in either the warm or the cool environment, or both, this could be accepted as evidence of increased blood flow sufficient to justify the procedure.

On this basis it was found that one could predict such a favorable result with over 90 per cent accuracy on the basis of the skin-temperature category into which the extremity fell, provided that, in the presence of obliterative vascular disease, the state of the main vessel pulsations and the collateral circulation were taken into consideration. The main vessel pulsations were divided into four groups. *Group 1* contains patients with no pulsations absent. In *group 2* one or all pulses are absent below the popliteal. In *group 3* the popliteal pulse was absent. In *group 4* the femoral pulse was absent. Similar pulse groups may be used for the upper extremity, but the number of arms having obliterated pulses are so few that we have not been able to take all of the pulse categories into consideration. The state of the collateral circulation was evaluated in a simple fashion. It was considered adequate if, after blanching on elevation, flushing of the toes on dependency commenced in twenty seconds or less. Filling of the veins on the dorsum of the foot in thirty seconds or less is also evidence of adequate collateral circulation, provided the valves in the veins are competent.

The following rules for the selection of cases for extremity sympathectomy may then be followed with confidence that the circulation will be increased sufficiently to justify operation. The only proviso is that, in the presence of obliterative vascular disease, the collateral circulation be adequate. These rules apply both to obliterative and vasomotor disorders and to upper and lower extremities:

1. No pulses absent: Sympathectomy may be performed if the extremity is in any skin-temperature category except 3D.
2. One or all pulses absent below the popliteal: Sympathectomy may be performed if the extremity is in any skin-temperature category except 2D and 3D.

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sympathectomy would be worth while. After operation a repetition of the studies revealed that the pattern had changed remarkably and the extremity was in category 3D. Plethysmography in such a case would reveal a nonpulsatile type of blood flow. Preoperatively, this extremity was in pulse category IV, but since the skin-temperature category was 1A, operation would be indicated (see Fig. 37).

in both environments; 3D is the least vasospastic category, the digital temperatures being well above room temperature in both environments. The 3D category is the one into which all extremities not having obliteration of main vessels or advanced changes in the digits will fall after sympathectomy. Many extremities in which obliterative vascular disease exists will also fall into this category after operation. Many upper extremities (60 per cent of normals) and occasional patients with typical Raynaud's phenomenon will also fall into this category. Only 20 per cent of normal lower extremities fall into the 3D category, while the majority fall into the B categories. This confirms what has often been pointed out, that the vasomotor tone is greater in the lower than in the upper extremity. Surface-temperature graphs of a 1A extremity before sympathectomy which was converted to a 3D extremity after operation are shown in Figure 36.

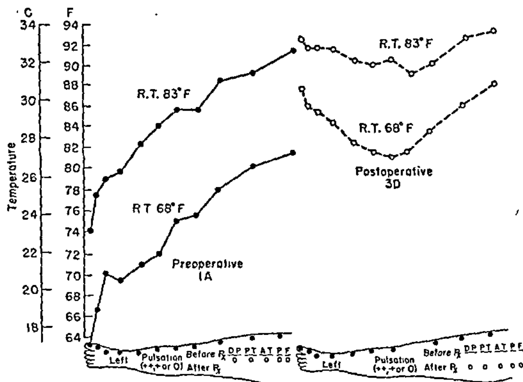


Fig. 36. Skin temperatures before and after lumbar sympathectomy for obliterative vascular disease with marked vasospasm

In this figure the skin-temperature readings apply to the points marked on the outline of the legs beneath The abbreviations used to indicate arterial pulsation: D P., dorsalis pedis, P.T., posterior tibial; A T., anterior tibial, P, popliteal; F, femoral.

This fifty-four-year-old male patient had extensive obliterative vascular disease due to arteriosclerosis. There were no palpable pulsations in any of the main vessels including the femoral. The skin-temperature studies prior to operation carried out in first a warm and, on another occasion, a cool environment indicate marked vasospasm. These studies placed the extremity in category 1A. Since the collateral circulation was satisfactory, one could predict with certainty that the physiological effect of

This method of study does not help in the further evaluation of excluded extremities in group 3 and 4 pulse categories, since the flow is nonpulsatile under all conditions of study. Blood-flow studies following venous occlusion at the base of the digits have not been found of help in this group. Goetz (1950) has reported that this method of study is helpful in the selection of cases for extremity sympathectomy in the presence of a nonpulsatile flow. In his cases venous occlusion was applied just distal to the knee. Further study of this group of extremities is in progress.

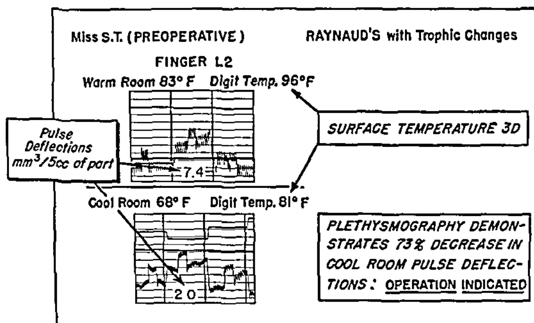


Fig. 38. Plethysmographic evidence indicating favorable response to sympathetic denervation.

This thirty-two-year-old female patient had typical Raynaud's disease with multiple-phase color changes of the digits of both hands on exposure to cold, with small ulcerations of the tips of several fingers of each hand She was highly incapacitated. All of the main vessel pulsations were normal; she was thus placed in the group 1 pulse category. The skin-temperature studies prior to operation revealed high temperatures of the tips of the digits in both the warm and cool environments, thus placing her in skin-temperature category 3D. As far as skin-temperature data are concerned, one cannot say that there is evidence of a sufficiently active vasoconstrictor mechanism to justify sympathectomy in extremities falling into the 3D category. However, the plethysmographic studies show a marked decrease in pulse deflections in the cool environment, sufficient to justify sympathectomy. The findings in both extremities were similar, and those pertaining to the left second finger are shown in this illustration. A bilateral upper thoracic sympathectomy with anterior root section was performed, with an excellent clinical result. One year postoperatively the pulse deflections in this extremity were 5.5 mm ^{3}/5 cc of part in both the warm and cool environments, indicating a complete denervation. Plethysmography is helpful in the selection of patients for sympathectomy in pulse categories 1 and 2 when the skin-temperature data do not give evidence of an active vasoconstrictor mechanism (see Fig. 37).

3. Popliteal pulsation absent: Sympathectomy may be performed if the extremity is in any skin-temperature category except 2D, 3D, 2C, and 3C.

4. Femoral pulsation absent: Sympathectomy may be performed if the extremity is in any skin-temperature category except 2D, 3D, 2C, 3C, 2B, and 3B.

These rules are diagrammatically presented in Figure 37.

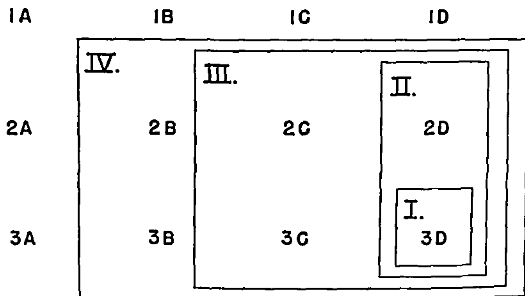


Fig. 37. Selection of cases for extremity sympathectomy on the basis of skin-temperature and pulse categories.

The twelve skin-temperature categories are shown ranging from 1A to 3D. The rectangles surrounding certain skin-temperature categories refer to the pulse categories. In the upper left-hand corner of each rectangle the particular pulse category is indicated. Operation may be performed in all skin-temperature categories *not* included within the corresponding pulse-category rectangle.

With regard to extremities falling into the excluded 3D and 2D skin-temperature categories for group 1 and 2 pulse categories, plethysmography is helpful in the selection of these cases for sympathectomy. Occasionally, patients with Raynaud's phenomenon of the upper extremities who have severe signs and symptoms will fall into the 3D category. Occasional lower extremities with early obliterative changes will fall into the 2D category. If the pulse volume is decreased 50 per cent or more in the cool environment below that noted in the warm environment, it is felt that operation is justifiable. An example of a patient having a marked reduction in pulse volume by plethysmography who had severe Raynaud's disease of the upper extremities, both of which fell into the 3D skin-temperature category without obliteration of pulses, is shown in Figure 38. This patient has had an excellent result from sympathectomy.

and tabetic crises may produce pain simulating symptoms of visceral origin. In older patients it is also best to take roentgenograms of the vertebrae to rule out spinal arthritis and metastatic malignancy. The opinion of an experienced psychiatrist is often of great value in the difficult differentiation between obscure visceral pain and a psychoneurosis. It must be remembered that many of these cases have the characteristics of the neurasthenic, because prolonged suffering and frequently associated addiction to drugs lower the sensory threshold as well as the patient's morale. When incurable visceral disease, such as aneurysm of the aorta or carcinoma of the stomach, is the cause of pain, and the only problem is to discover the pathways of its transmission and the best way to interrupt them, procaine injection is indicated from the start.

The technique of injection for the study of intractable pain differs in no way from that of diagnostic paravertebral procaine block in vasomotor conditions. Selective blocking of the visceral afferent nerves is of particular value in localizing the segments over which pain is referred and in deciding whether it can be permanently interrupted by sympathectomy or should be attacked by more radical procedures on the spinal cord. The test is also of great assistance in differentiating individuals with true visceral pain from the psychoneurotic group.

In cases of abdominal pain of unknown origin a useful preliminary method of localization has been suggested by Alvarez (1931). This consists in administering a high spinal injection of procaine and in determining the level of skin anesthesia at the moment the pain disappears. In the case of the neurotic patient, total anesthesia of the trunk may have no effect on the patient's sensation of pain. In the real sufferer, however, the pain characteristically ceases as anesthesia reaches a certain segment and reappears at the same level when it wears off.

Other clues to the segments over which visceral pain enters the spinal cord can be gained from observation of areas of skin hyperesthesia or abnormal sweating, as well as from a knowledge of visceral innervation (Table II, Chap. VI). Pain referred to the right upper quadrant may arise from the biliary passages; under these circumstances it can be interrupted by blocking the seventh to ninth thoracic ganglia. If the pain comes from the region of the kidney, injection of the twelfth thoracic and upper two lumbar ganglia will interrupt it. It is important to limit the amount of procaine injected in the region of any ganglion to 3 cc, since large amounts may spread over a wide area and give very misleading results. If the injection of two to four ganglia is unsuccessful, the process should be repeated at a later date and at a higher or lower level. Even if successful,

The foregoing discussion is based upon the philosophy that in order to be effective or worth while it is not necessary that sympathectomy be confined to extremities exhibiting increased vasomotor activity. It is necessary only that vasoconstriction be active enough to decrease blood flow sufficiently to warrant elimination of this factor. These rules for the selection of patients for extremity sympathectomy are designed to pick out those cases where one can be quite certain that operation will be worth while on the basis of a rise in digital temperature of 8° F (4.4° C) or more after operation. In some cases the temperature will rise as much as 25° F (14° C). Extremities which are excluded still might be helped, but it is clear that the result is highly problematical in this group. If one still chooses to operate upon these cases, one is at least aware of the fact that a good result is unlikely. The most important contraindication to sympathectomy is inadequate collateral circulation in the presence of obliterative vascular disease. It is in this group of patients that sympathectomy will not only do no good but may be harmful.

C. LOCALIZATION OF VISCEROSENSORY PATHWAYS BY DIAGNOSTIC INJECTIONS

Paravertebral injection of the sympathetic ganglia with procaine is just as applicable to the study of afferent nerve pathways as it is to the quantitative determination of vasomotor activity. Lawen (1923) and von Gaza (1924) first utilized this as a diagnostic aid in the investigation of the pathways of visceral pain. By its use Mandl (1925*B*) was able to define more exactly the afferent cardiac nerves. In this country, however, little attention was paid to these excellent articles before the reports of Archibald (1928) and Scrimger (1929). Since the publication of their papers an increasing appreciation of the diagnostic value of this procedure has been shown by frequent reports in the surgical journals. From the Massachusetts General Hospital, White (1930*A* and *B*) and Mixter and White (1931) have shown its value in neurological localization of unusual forms of vascular and visceral pain. Valuable papers describing its application and uses have been written by Woodbridge (1930), Alvarez (1931), Flothow (1931), Abbott (1932), W. K. Livingston (1938*B*), and Homans (1940).

Before discussing the technique of diagnostic injection for the study of visceral pain, it is necessary to warn against its indiscriminate use in obscure painful conditions. All other diagnostic and therapeutic methods must be tried first. A lumbar puncture must always be performed to make certain that there is no disease of the spinal cord, as tumors, arachnoiditis,

pathectomized area become inactive. This subject has been discus detail by List and Peet (1938*A*, *B*, *C*, and *D*), by Roth (1937 most recently by Hyndman *et al.* (1941*B* and 1948). After cervicotl ganglionectomy the area of anhidrosis generally involves the corre ing side of the head, the arm, and the upper thorax down to the re the second or third ribs. When the lumbar ganglia have been re sweating disappears at a variable point between the groin and th excepting an area of variable size on the anterior aspect of the (see p. 31). The demonstration of the presence or absence of sv on the skin surface is a simple and effective method for determining the completeness and extent of sympathectomy (Fig. 39).

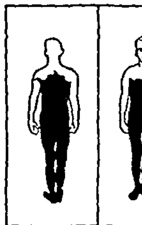


Fig. 39. Reflex sweat After bilateral glionic thoracic sym tomy there is c anhidrosis of the head extremities, and the T4. Below this level, or increased reflex s is indicated by the starch reaction.

A satisfactory method for testing the activity of the sweat glands is to expose the subject to a temperature of about 51° C (125° F) in a heating cabinet, as described above. Normally innervated glands respond by active secretion of sweat; denervated glands remain quiescent. Some investigators have advocated the use of pilocarpine nitrate (tartrate or hydrochloride) in doses of 3 mg (1/20 gr) injected subcutaneously, with repetition of the dose until generalized profuse sweating and salivation result. We have not used this test because it is very disagreeable to patients and because it does not discriminate between normally innervated glands and those decentralized by preganglionic denervation (cf. Simeone, Mentha, and Rodrigues, 1951).

While moderate degrees of sweating are visible or can be made sense of touch, there are several very simple physicochemical m which can detect even the slightest degrees of sweating:

Cobalt-blue Papers. Sheets of filter paper are dipped in cobalt ch solution and dried on a steam radiator. The pink hydrate ($CoCl_2$-6 H_2O) becomes blue when it loses its water of crystallizati reacquires it upon contact with the slightest dampness to become again. Strips of the dried treated paper can be laid onto the areas tested and kept in place by adhesive plaster or Scotch tape.

Starch-iodine Tests. Sheets of filter paper are impregnated with cent starch solution and dried. The dried paper is then covered

the test should be repeated and verified on several occasions. So great is the power of suggestion in the neurotic type of patient, that the pain may be temporarily relieved because the patient feels that something dramatic is being done to him. An operation performed on such a false premise will certainly fail to benefit or may even aggravate the pain. In order to rule out the psychoneurotic and the malingerer, inert salt solution instead of procaine should be injected at the beginning of one of the tests without the patient's knowledge. If this fails to influence the pain, but the patient is relieved as soon as procaine is added, then the chances are all in favor of permanent relief following sympathectomy or a successful injection of alcohol.

It is obvious that these methods are trying, both to the patient and to the surgeon, yet any amount of effort on the part of the latter, and even a considerable degree of discomfort to the former, are better than a useless operation.

In the case of pain from the head, arm, or leg, the sympathetic innervation to these regions can usually be blocked without anesthetizing their somatic sensory nerves, as these principally enter the cord cephalad or caudad to the thoracolumbar white rami. In the thorax and abdomen, however, infiltration of procaine around the sympathetic ganglia may result in a simultaneous anesthesia of the corresponding spinal nerves. In these situations, it must be recalled that pain arising in the parietal pleura or peritoneum, as well as in other parts of the thoracic or abdominal wall, can be relieved only by section of the posterior roots or the spinothalamic tract. Pain in the viscera themselves is entirely interrupted when the correct visceral afferents which run in the sympathetic trunks are blocked, and relief is sure to follow resection of these ganglia or their destruction with alcohol, unless the disease has spread beyond the viscus proper and has involved somatic nerves in the parietal peritoneum or pleura. This, of course, is the case in advanced malignant disease, and in such cases sympathetic denervation is generally useless.

The application of this method to the study of various specific types of visceral pain will be taken up in detail in later chapters.

III. Postoperative Tests to Determine the Completeness of Sympathectomy or Evidence of Regeneration

A. SWEATING TESTS

When the peripheral sympathetic neurons, which include sudomotor fibers, are paralyzed by block or operation, the sweat glands in the sym-

pathectomized area become inactive. This subject has been discussed in detail by List and Peet (1938*A*, *B*, *C*, and *D*), by Roth (1937), and most recently by Hyndman *et al.* (1941*B* and 1948). After cervicothoracic ganglionectomy the area of anhidrosis generally involves the corresponding side of the head, the arm, and the upper thorax down to the region of the second or third ribs. When the lumbar ganglia have been removed, sweating disappears at a variable point between the groin and the knee excepting an area of variable size on the anterior aspect of the thigh (see p. 31). The demonstration of the presence or absence of sweating on the skin surface is a simple and effective method for determining the completeness and extent of sympathectomy (Fig. 39).

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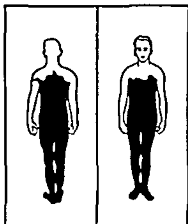


Fig. 39. Reflex sweating test. After bilateral preganglionic thoracic sympathectomy there is complete anhidrosis of the head, upper extremities, and thorax to T4. Below this level, normal or increased reflex sweating is indicated by the iodine-starch reaction.

While moderate degrees of sweating are visible or can be made out by sense of touch, there are several very simple physicochemical methods which can detect even the slightest degrees of sweating:

Cobalt-blue Papers. Sheets of filter paper are dipped in cobalt chloride solution and dried on a steam radiator. The pink hydrated salt ($CoCl_2$-6 H_2O) becomes blue when it loses its water of crystallization but reacquires it upon contact with the slightest dampness to become pink again. Strips of the dried treated paper can be laid onto the areas to be tested and kept in place by adhesive plaster or Scotch tape.

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A. SWEATING TESTS

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B. REFLEX VASOMOTOR RESPONSES

As already discussed, vasoconstriction in the periphery is the physiologic response to exposure to a cold environment and is brought about by activity of the vasomotor sympathetic fibers especially in the digits, hands, and feet. The digital skin temperature then approaches that of the room, and in some cases of Raynaud's disease it drops below that of the room. The temperature of denervated extremities, however, remains at the average maximal vasodilatation level, and this fact is used as a sensitive test for the completeness of sympathetic denervation. We have considered that when upon exposure to an environmental temperature of 68° F (20° C) the digital skin temperature drops below 90°F (32° C), this constitutes presumptive evidence of some vasoconstrictor activity. The evidence is confirmed by obtaining a rise in the skin temperature when the appropriate nerve fibers are blocked with procaine. If the skin temperature does not rise to the average vasodilatation level, the observation is then attributed not to vasomotor nerve activity but to organic occlusive disease of the arteries. Methods other than nerve block can be used to release the blood vessels from vasomotor control, as already described, but we have found the injection of procaine into the paravertebral ganglia or the peripheral nerves the most reliable (Simmons and Sheehan, 1937 and 1939; Smithwick, 1940*A*; Felder *et al.*, 1949).

Even more sensitive than careful measurements of the skin temperature are the digital plethysmographic tests, using photoelectric techniques (Hertzman, 1937 and 1938; Hertzman and Dillon, 1940; Finesinger *et al.*, 1939; Smithwick, 1940*C*), or ingenious methods for recording minute changes in volumes and pressures (Bolton *et al.*, 1936; Goetz, 1948*A*; Burch, 1947). Reflex responses to external cold, noise, alarm, etc., are prompt and are clearly seen. They can be blocked by infiltrating the appropriate nerves with procaine. Reflex changes in responses to various stimuli detected by the photoelectric cell are illustrated in Figure 48.

In the follow-up study of patients after sympathectomy, one or more of these methods for detecting vasomotor activity must be used if the follow-up data are to be of value. An appreciable degree of vasomotor recurrence may exist and be easily demonstrable by these laboratory methods, when clinical observation alone would consider an area completely denervated.

solution of iodine in absolute alcohol. This is evaporated off rapidly on a steam radiator or hot plate. The paper so prepared has a light-brown color, and upon contact with the slightest degree of moisture it turns a deep blue, almost black. The paper can be used in the same way as the cobalt-blue paper.

A convenient starch-iodine method for mapping large areas of the body was described by Victor Minor (1928). To 900 cc of dilute tincture of iodine (1.5 per cent), 100 cc of castor oil are added. This solution is painted onto the skin and, after evaporation, leaves a thin film of oil and iodine. Starch powder dusted over the area adheres to the oil, and wherever any moisture appears it turns a deep blue-black color. One advantage of this test is that the area of sweating stands out clearly on the photographic plate (Fig. 39).

Quinizarin Powder. The most convenient of the physicochemical tests for detecting minimal degrees of sweating is that employing quinizarin powder. This is dusted very lightly onto the areas to be studied, and sweating is then stimulated by heating the body or, in special circumstances, by the administration of pilocarpine. The powder, a light gray when dry, turns a blue-black when moist.

Cutaneous Resistance. The resistance offered by the skin to passage of a current through it is conditioned by the state of its sympathetic nerve supply. The dry scaly layer of the epidermis is an excellent insulation until moistened, when it conducts a current fairly readily. The technique for studying skin resistance and the interpretation of results have been discussed by Darrow (1929), Richter (1929), and C. Landis (1932). A new portable instrument has been described recently by Whelan (1950).

The skin resistance is not only high after sympathectomy, but it is also steady. It remains at a constant level despite external stimuli which normally excite sudomotor activity. The technique is therefore a very sensitive one for ascertaining the completeness of sympathectomy and for detecting the earliest signs of regeneration ("psychogalvanic reflex"). By means of specially designed apparatus for measuring and recording the skin resistance and its variations, Richter (1929) and his associates (Richter and Woodruff, 1941) have made extensive studies of the effects of nerve lesions and of different types of sympathectomy on cutaneous resistance. After sympathectomies for Raynaud's disease, Felder *et al.* (1949) found that the return of sudomotor and vasomotor activity are usually concomitant despite the fact that these modalities are carried by different neurons.

IV. Changes after Sympathectomy

Certain phases through which an extremity passes after preganglionic sympathectomy deserve a word of comment. If daily surface-temperature and skin-resistance measurements are made, a consistent series of changes will be observed during the first three weeks. These are illustrated in Figure 40. The preliminary high level of surface temperature and skin resistance

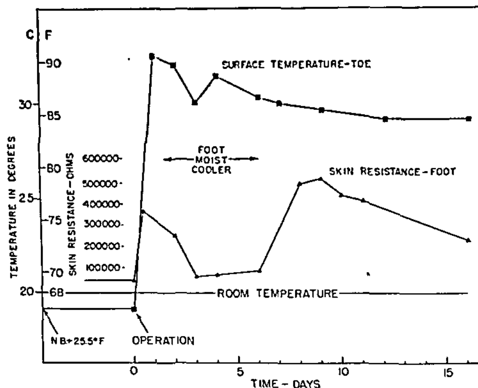


Fig. 40. Surface-temperature and skin-resistance changes after preganglionic sympathectomy.

Daily surface-temperature and cutaneous-resistance readings, plotted for two weeks after complete denervation of the lower extremity. The curves are similar to those noted for the upper extremity. The phase of lowered temperature and cutaneous-resistance levels accompanied by clinical evidence of moisture and coolness is brought out (From Smithwick, R H. "Surgical intervention on the sympathetic nervous system for peripheral vascular disease." *Arch. Surg*, 1940, 40: 286–306, courtesy of American Medical Association, Chicago.)

which is maintained for the first few days after operation undergoes a curious depression which occurs, as a rule, from the third to the fifth or sixth day. This is accompanied by the sudden onset of sweating, color changes, and coolness of the extremity. This phenomenon may be very marked or slight and evanescent. The change is usually noticed first by the patient and may be so marked that it makes one wonder if the extremity in question was *really denervated*. These signs disappear after thirty-

C. PILOMOTOR TESTS

The erector muscles in the hair follicles are composed of smooth muscle and are innervated by the sympathetic system alone. When this system is interrupted or paralyzed, goose flesh can no longer be produced spontaneously. The reaction can be readily produced normally by exposure of the whole body to cold or exposing only parts of it, such as by applying ice to an individual's spine. Sudden immersion into a hot bath can also elicit the reflex. Contraction of these muscles can be excited locally by direct electrical stimulation of an area of skin with bipolar electrodes, as described by T. Lewis and Marvin (1927). While the reflex response disappears when any portion of the reflex arc is destroyed (somatic sensory nerve, pre- or postganglionic neurons), the response to direct stimulation disappears only when the postganglionic neurons have degenerated. Thus no pilomotor reflex can be evoked in either the arm or the hand after cervicothoracic ganglionectomy, but the direct response will still be present when the upper extremity is denervated by preganglionic section. The same test may be applied to activity of the sweat glands (Simeone, Mentha, and Rodrigues, 1951).

D. REACTION TO ADRENALINE

In Chapter V it has been demonstrated that, as the sympathetic nerves to a part degenerate, the denervated smooth muscle of the arteriolar walls becomes hypersensitive to adrenaline. As a result, injection of 1 part of adrenaline in 250,000 parts of normal saline (injected intravenously at the rate of 40 to 60 drops per minute) will cause striking vasoconstriction in extremities after complete degeneration of their sympathetic nerves. For smooth muscle in general, this response is maximal after a postganglionic operation and less after a preganglionic denervation or decentralization. In the normally innervated extremity, or after incomplete denervation, the vasoconstrictor response is small unless excessive amounts of adrenaline are used or the drug is injected intra-arterially, as reported by Fatherree, Adson, and Allen (1940). Simeone and Felder (1951), using a plethysmographic method, demonstrated a clear-cut increased adrenaline sensitivity of denervated digital blood vessels as compared with comparable undenervated digits. While the adrenaline responses after postganglionic sympathectomy in various species of animals (White *et al.*, 1936; Ascroft, 1937) are greater than after preganglionic sympathectomy, this phenomenon is of relatively little, if any, clinical importance in man (cf. Felder *et al.*, 1949).

of the second or beginning of the third week. Simmons and Sheehan (1939) observed that when recurrence of signs and symptoms occurred after sympathectomy for Raynaud's disease, the previously increased sensitivity to adrenaline had returned to normal. This interesting observation suggests that the recurrences seen were due to regeneration of nerve fibers, for it fits the observation made in animals (Simeone, 1937) that supersensitivity disappears as regeneration occurs (Fig. 42).

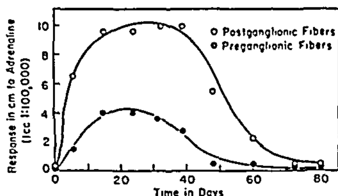


Fig. 42. Return of supersensitivity of denervated smooth muscle to normal with regeneration of the nerve supply.

The responses of the nictitating membranes of a cat to intravenous injection of 2 to 0.25 cc adrenaline, 1:100,000, are shown at intervals after postganglionic denervation of the right nictitating membrane and preganglionic of the left. Ordinates: responses in centimeters X 19. Abscissas: days after denervation. (Reproduced from Simeone, F. A. "The effect of regeneration of the nerve supply on the sensitivity of the denervated nictitating membrane to adrenine." *Amer. J. Physiol.,* 1937, 120: 466–474, courtesy of American Physiological Society, Washington.)

It becomes apparent that important changes are taking place in the periphery during the first fortnight after sympathectomy. During the third week a slight, gradual fall in skin temperature and skin resistance occurs. The color of the skin approaches normal, losing some of the pinkness which had been due to the maximal early arteriolar dilatation. By the end of this time the extremity becomes stabilized, and no further changes are found until there is recurrence of vasomotor activity. Clinical symptoms do not recur without signs of vasomotor activity and usually sudomotor activity as well (Felder *et al.,* 1949).

The maximal surface temperature of the skin after sympathectomy (and presumably the maximal blood flow) is present on the first day after operation. During the early postoperative period the skin temperature is likely to be lowest between the third and sixth postoperative days. It is important to bear this point in mind when sympathectomies are planned to aid the residual circulation in connection with operations for lesions

six to forty-eight hours. Occasionally, they last only a few hours. If, during this phase, a peripheral nerve block is done, a rise in surface temperature as much as 10° F (5.5° C) may be obtained. A number of patients have been studied during this phase. Although skin resistance is temporarily reduced, reflex variations in resistance and vascular responses are absent. This suggests that the spontaneous activity arises in the decentralized sympathetic ganglia. It may represent excitation of the ganglion cells by acetylcholine, liberated by the degenerating preganglionic axons. In a few patients, measurements of the volume of the pulse wave have been made before and for several days after sympathectomy. There is a decrease in the amplitude of the pulse wave which approaches the preoperative level and remains low in spite of the fact that the skin temperature rises again from the low early postoperative phase (Fig. 41). A return of

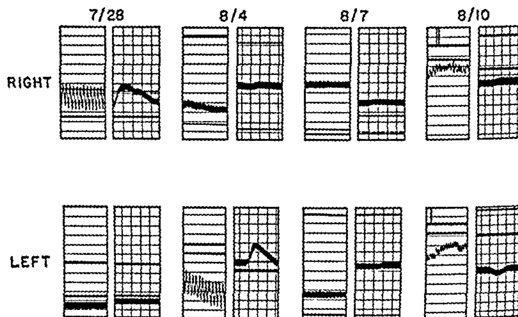


Fig. 41. Burch-Winsor digital plethysmograph

Records (slow and fast speeds) from a patient with Raynaud's disease who had thoracic preganglionic sympathectomy on the right on 6/27/49 and on the left on 8/3/49. Note the return of the pulse volume to nearly preoperative levels after a marked immediate postoperative increase.

the rate of blood flow to the preoperative level about two weeks or less after sympathectomy has been reported by Barcroft and Walker (1949) for the hand and by Lynn and Barcroft (1950) for the foot.

If one makes repeated measurements of sensitivity to adrenaline, it will be seen that this sensitization phenomonen makes its appearance about the end of the first week after operation and reaches its height at the end

PART II

Introduction

The following chapters in Part II are concerned with the role of sympathectomy in modifying abnormal activity on the part of smooth muscle and glands, faulty visceral function, and intolerable pain. In connection with visceral pain, the thoracolumbar and sacral divisions of the autonomic system are treated as a subject of major importance because the afferent fibers, although strictly speaking a part of the somatic system, reach their destination via the sympathetic trunks and the splanchnic and hypogastric plexuses. While it is seldom feasible to resect the sympathetic nerves to a single organ, like the colon, selectively, a thorough knowledge of neuroanatomy often makes it possible to spare important fibers to neighboring viscera.

The purpose of this section is to point out those conditions which are suitable for sympathectomy and equally those which are not. No particular effort will be made to discuss the purely medical aspects of these diseases nor their differential diagnosis, as this would constitute a useless repetition of textbooks on general medicine and neurology. It will be noted that the antiquated doctrines of sympathicotonia and vagotonia are never mentioned. Furthermore, there is no chapter on tumors. With the rare exception of paroxysmal hypertension from a secreting adenoma of the adrenal medulla, these neoplasms produce no specific physiological phenomena and are therefore of no particular interest in this field. Information on this subject must be sought in the texts on neoplastic disease.

The reader will find in the following chapters that the three authors are not always of the same opinion, particularly concerning the treatment of such still-unsettled problems as peripheral vascular disease and hypertension. We have been careful to state where and how we differ, and we hope that these divergencies of opinion will not prove disturbing. If three investigators fail to disagree in at least some of the details of their subject, it is likely to mean either that the field has become a static one or that compromise has been stretched to the point of obscuring individual opinion.

of the large arteries. If sympathectomy is done as a preliminary procedure, the operation upon the arteries should be delayed until at least six days later.

During the late postsympathectomy period, when the circulation in the extremity has become stabilized, procaine block of the peripheral nerves may cause a temperature rise of 0.9 to 1.8° F (0.5 to 1.0° C) in the skin supplied by them. This may be due to a slight residual innervation following the sympathectomy or to continued spontaneous activity of the decentralized ganglion cells (Govaerts, 1936). It is of no clinical significance. The curious phenomena noted in the early weeks after sympathectomy have been described in some detail by Smithwick (1940C).

CHAPTER VIII

The Sympathetic Nerves in Peripheral Vascular Disease

I. Raynaud's Disease and Allied Vasomotor Disorders

DEFINITION

In 1862 Maurice Raynaud described a disease entity characterized by symmetrical impairment of the circulation in the fingers and toes with phasic color changes, a condition which often progressed to ulceration of the finger tips and gangrene without occlusion of the larger arteries. His early description, in which he segregated this syndrome from a large group of peripheral gangrenes concerning which little was known, has become a medical classic. His observations were so complete and his deductions from them so judiciously drawn that little was added to them in the next sixty years. The disease has appropriately come to be called by his name. His two articles (1862 and 1874) should be read in full by all who are interested in peripheral vascular disease.*

In many past and current articles the term Raynaud's disease has been loosely applied to a great variety of circulatory disorders.† In order to exclude extraneous conditions the following definition has been formulated by the peripheral vascular clinic of the Massachusetts General Hospital:

> Raynaud's disease is a form of peripheral vascular disturbance caused by tonic contraction of the smaller arteries in the extremities. During the early uncomplicated stages of the disease there are no obvious pathological changes in the walls of the arteries. The disease commonly involves symmetrical areas in the hands and feet, causing circulatory stasis with periods of cyanosis or pallid asphyxia. The severe cases go on to dry gangrene of the phalanges. The spasm is intermittent and occurs on exposure to cold or emotional stimuli; it involves only the terminal arteries, while the main vessels continue their normal pulsations. Frequently these patients complain of excessive perspiration,

* A good English translation by Thomas Barlow is available, published by the New Sydenham Society, Volume CXXI.

† An excellent classification of the various conditions which lead to symmetrical gangrene of the digits has been proposed by T. Lewis and Pickering (1934).

ited to the hands and feet, with the greatest reduction of blood flow in the fingers and toes. In a warm environment the circulation may appear normal. Each case, however, has a critical temperature below which vasospasm sets in. Below this thermal threshold the hands and feet behave like the extremities of a cold-blooded animal. The critical temperature varies with the intensity of the disease. In a mild case it may be as low as 65° F (18° C); in the severe instance, as high as 80° F (26° C). In the former the patient has no complaints in a normally heated room and gets along reasonably well out of doors with warm gloves. In this stage recovery of peripheral circulation is rapid and complete on warming, whereas in the advanced stage it takes place only slowly and incompletely even above 80 degrees. For this reason the severe case cannot be comfortable even in an overheated room.

Phasic color changes are characteristic of the disease. These come on whenever the temperature falls below the critical level for the particular patient. Cyanosis, which may vary in hue from slate gray to purple, appears relatively early in the course of the disease. In advanced cases, where normal circulation is never fully restored, some degree of cyanosis persists most of the time. In the milder cases, which have not progressed to obliterative changes in the arteries, the discoloration disappears rapidly on warming. The attacks of dead-white blanching of the skin are seen much more frequently in the fingers than in the toes. They begin symmetrically in the finger tips of both hands and spread to involve the full length of the fingers. The thumbs often are not involved. In the stage of asphyxia the fingers may be numb or moderately painful; during recovery from an attack the patient usually complains of either burning or a pins-and-needles sensation. Except in the severest cases normal circulation can be restored, and the patient then becomes symptom free.

In the severe forms of Raynaud's disease normal circulation can be attained only at such high temperatures that the patient lives in a constant state of discomfort and partial digital asphyxia. One woman said that she could get her feet comfortably warm only by putting them up before an open oven door. The result of such chronic anoxemia is terminal ulceration of the phalanges with fibrosis of the skin and subcutaneous tissue, a process which eventually ends in dry gangrene of the finger tips or a form of scleroderma.

Besides the phasic color changes and the lack of involvement of the main arteries, Raynaud's disease is characterized by its extreme symmetry. Corresponding digits become involved in the upper and lower extremities, most commonly all the toes and all the fingers except the thumbs. Rarely the

which is also limited to the extremities. The disease most commonly occurs in young individuals with hyperirritable nervous constitutions.

While wishing to exclude all instances of primary obliterative disease of the arteries from this discussion, we can see no purpose in differentiating between classical Raynaud's disease, described above, and such allied vasospastic conditions as acrocyanosis. In the former, cyanosis alternates with pallid asphyxia, while in the latter the extremities are constantly blue, as well as abnormally cold. Both conditions have a common underlying cause, and both can be relieved surgically by cutting the vasoconstrictor pathways. For these reasons acrocyanosis will be considered in this chapter on the vasomotor disorders as a variety of Raynaud's disease and not as a separate clinical entity.

Examination of the peripheral circulation of a large number of normal individuals will disclose occasional cases of excessively cold, moist hands and feet. All of us are acquainted with such individuals, and if we observe them closely we will note that their hands become dusky to cyanotic in the cold. When they grasp a cold object like the steering wheel of an automobile on a cold day or a milk bottle from the refrigerator, their fingers may become abnormally white. During the winter months they are forced to wear bedsocks at night, and even then may have difficulty in keeping their feet warm. Characteristically, these are young, emotional individuals, and most frequently women. Ordinarily, they complain of "poor circulation" and make the best of this handicap. Most often this condition does not advance, but rather diminishes with increasing age and the general reduction in sympathetic activity that goes with it. However, in following a number of these individuals over a period of years, we have seen some progress to typical full-fledged Raynaud's disease. It has impressed us that this has often followed a period of intense emotional strain, such as divorce, the death of a near relative, or financial failure. We have observed this train of events too often to feel that it can be a mere coincidence. From these observations we have come to believe that the common clinical syndrome described constitutes a prodromal form of Raynaud's malady.

Raynaud's disease is far more common in women than in men, its incidence in the female sex being approximately ten times more frequent than in the male. It generally appears between puberty and menopause, and is rarely seen in childhood or old age. A most valuable clinical study of the subject has been written by E. V. Allen and G. E. Brown (1932).

The usual case of Raynaud's disease shows no abnormality of the larger peripheral arteries, and the radial pulses, as well as the dorsalis pedis and posterior tibial arteries, can be easily palpated. Obvious vasospasm is lim-

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ears, the tip of the nose, and, in one case seen at the Massachusetts General Hospital, the tongue have shown typical attacks. Raynaud (1874) also described attacks of intermittent constriction of the retinal vessels with blurring of vision.

Excessive sweating is a common feature of the disease and in the early stages may be the patient's chief cause of complaint. The hands and feet are constantly moist and at times literally drip drops of sweat. This is particularly striking in the younger patients, who frequently comment themselves on the aggravation of this annoying condition when they become excited or emotionally upset. In the older patients or in the late stages of the disease with sclerodermatous changes, hyperhidrosis is frequently absent.

Great care must be taken in making the diagnosis of Raynaud's disease to rule out cases of primary arterial obliteration, especially in men. When the involvement is not perfectly symmetrical, and especially when the main vessels at the wrist and ankle cannot be felt, simple vasospasm should be doubted. A number of cases reported by Raynaud himself should obviously be excluded from this category, and the literature abounds in reports of cases of thromboangiitis obliterans and arteriosclerosis masquerading under the diagnosis of Raynaud's disease. We have several times been impressed with cases of perfectly symmetrical ischemia and phasic color phenomena appearing in old age. In these instances the vasospastic phenomena have developed with unusual rapidity, and increased sweating has been absent. Arteriosclerosis can be diagnosed by X-ray evidence of calcified vessels and the failure of full vasodilatation after diagnostic procaine block. The fact that at times arteriosclerosis may closely simulate Raynaud's disease has not been sufficiently emphasized and adds considerably to the difficulty of accurate diagnosis.

Other disorders may be preceded by Raynaud's phenomena affecting the digits of the extremities. Thus, as we have followed these patients over the years, it has become apparent that, in some, multiple-phase color changes were precursors of other diseases such as rheumatoid arthritis, disseminated lupus, dermatomyositis, and generalized scleroderma. When originally seen there was no indication of the presence of these generalized disorders, and the patients appeared to have Raynaud's disease. This, of course, does not prove that Raynaud's phenomena are an early part of these other diseases, but it should lead one to suspect that about 10 per cent of cases exhibiting multiple-phase color changes will eventually prove to have them. The disease which is most likely to be present or to develop within a year after the onset of peripheral vasomotor phenomena is rheumatoid arthritis. In fact, it

was undoubtedly present and overlooked at the time sympathectomy was performed in several of our patients. Some of these cases had a stormy postoperative course with a marked febrile response, the cause of which was not apparent at once until pericarditis or other manifestations of an acute flare-up of the rheumatic process clarified the situation. It is therefore wise to suspect the presence of this disease in cases with Raynaud's phenomena of less than one year's duration. In other cases, particularly those which developed generalized scleroderma, it was not apparent for five to ten years after sympathectomy that this underlying disease process existed.

PHYSIOLOGY

The role of the vasomotor system is to regulate body temperature and to maintain an adequate supply of blood to the muscles and internal organs. Its action as a thermal regulator is carried out by cutaneous vasoconstriction on exposure to cold and by vasodilatation in hot surroundings. Cutaneous vasodilatation also serves to eliminate excess body heat produced by muscular exercise or other circumstances which increase the metabolic rate. Under resting conditions 76 per cent of the body heat lost is eliminated by radiation and conduction from the skin, the remaining 24 per cent by vaporization of water from the skin and lungs. Besides cold, pain or intense emotions of fear and anger are also capable of stimulating reflex vasoconstriction, whereas such emotions as shame and embarrassment result in vasodilatation.

Maddock and Coller (1933) have demonstrated the relative importance of the arms and legs in carrying out reflex changes in vasomotor tone. They have pointed out that the shift of blood to the surface of the body as a part of the thermoregulatory response is not uniform in all parts of the skin, but that actually there is a much greater transfer to the extremity surface than to that of the head and trunk. Another point which they have emphasized is the surprising fact that the extremities make up 65 per cent of the surface area of the body (arms, 14 per cent; hands, 6 per cent; legs, 38 per cent; feet, 7 per cent). Loewy (1914) has estimated that, per meter of body surface, heat dissipation is greatest in the arms, next greatest in the legs,* and least in the trunk, the extremities giving off not far from 75 per cent of the total. With these data in mind, one would expect a vasomotor neurosis to affect primarily the hands and feet.

From the time of Raynaud's original description it has been recognized that the lumen of the arteries is unobstructed in the early uncomplicated

* Taken part for part, most heat is lost from the legs because of their size.

stages of the disease. The site of vasospasm is not in the larger arteries, which characteristically maintain their pulsation throughout the attack, but in the digital arterioles. E. M. Landis (1930), by an ingenious method, was able to make direct measurements of capillary blood pressure. During periods of normal circulation this amounts to 40 mm of mercury, but during the asphyxial stage it may fall as low as 5 mm. The slowness with which capillary pressure rises when venous congestion is produced by a tourniquet during an attack, and the rapidity with which it falls on release, show that the spasm is situated on the arterial rather than on the venous side of the capillary network.

The shifts in arteriolar blood flow during the phasic color changes in Raynaud's disease have been thoroughly investigated by T. Lewis (1929*B*) and Lewis and Landis (1930). In the stage of pallid asphyxia there is only intermittent leakage of blood through the intensely constricted arterioles; with lesser intensity of spasm, varying degrees of acrocyanosis are manifest, depending on the reduction of the red, oxygenated form of hemoglobin. The degree of dissociation of the oxygen-carrying pigment molecule depends primarily on the metabolism of the tissues and the speed of its passage through the capillary loop, also to a certain extent on the temperature. *Below 50° F (10° C) oxyhemoglobin does not dissociate easily and tissue* metabolism is at a minimum, so that hands dipped in ice water may remain pink. Lewis points out that 59° F (15° C) is the most suitable temperature to bring out the cyanotic hue, as at this point vasospasm is marked and oxyhemoglobin still dissociates readily into reduced hemoglobin.

PATHOLOGY

Vascular Pathology. Cassirer, quoted by Leriche and Fontaine (1932*B*), perfused the peripheral arteries in an autopsy on a case of Raynaud's disease and showed them to be normally permeable. Recent arteriographic studies have corroborated this early observation, so that it is now generally admitted that there is no permanent narrowing of the peripheral vessels in early Raynaud's disease. However, in the stage of chronic acrocyanosis and long-continued digital asphyxia, very definite pathological changes set in. Spurling, Jelsma, and Rogers (1932), as well as Leriche and Fontaine (1932*B*) and Learmonth (1939), have taken photomicrographs of the digital vessels in such advanced cases (Fig. 43). These vessels show the organic changes of an obliterating endarteritis and are indistinguishable from those seen in long-standing Buerger's disease. With the sclerodermatous changes that are not infrequently seen in the late stages of Raynaud's disease, the digital vessels are compressed by the constricting scar which

invades the skin and subcutaneous tissue. In advanced sclerodactyly, diagnostic procaine block fails to produce any noteworthy increase in blood flow, and sympathectomy cannot be expected to produce improvement. Lewis (1938*A*) compared the digital vascular pathology of warm-handed

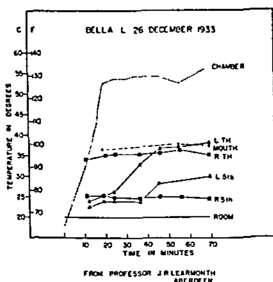




Fig. 43. Postoperative vasodilatation test and photomicrographs of digital arterioles in a patient with advanced Raynaud's disease.

Skin-temperature chart, after right upper thoracic sympathectomy, shows full vasodilatation of thumb but no improvement in circulation of fifth finger. On the unoperated left side the thumb develops complete vasodilatation on heating the body, but the fifth finger shows only a slight response. The photomicrographs are sections of the digital artery in the right fifth finger after amputation. They show areas of complete occlusion and recanalization (Reproduced through courtesy of Professor Sir James Learmonth, Edinburgh.)

individuals with that seen in various stages of Raynaud's disease. He found that intimal thickening is the rule in the former group from the age of 50 onward, and is no more marked in the earliest stages in the latter group in patients of comparable age. He found no evidence of hyperplasia of the media in early stages of Raynaud's disease. In more advanced cases thrombotic obstruction of the digital arteries in various stages of organization is the rule.

The capillaries in advanced Raynaud's disease commonly show a characteristic pattern which consists of a striking elongation, tortuosity, and

dilatation of the loops seen in the nail bed (Fig. 44). During an attack these varicosed loops are crammed full of stagnant erythrocytes. After sympathetic denervation the dilated capillary loops contract to the normal straight, narrow type, and the stagnant clumps of erythrocytes are restored to active circulation.

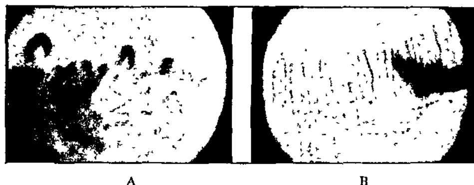


Fig. 44. Dilated tortuous capillaries seen in Raynaud's disease (A) compared with those in a normal individual (B).

Skin and Subcutaneous Tissue. In the early stages of Raynaud's disease there is no noticeable change in the skin After prolonged and recurrent periods of asphyxia, however, superficial ulcers appear at the tips of the fingers, which at first tend to heal readily in warm weather. As the disease advances, these areas of necrosis may extend down to the bone (Fig. 45). The growth of the nails becomes extremely sluggish, and they may show extraordinary thickening and other trophic changes. Chronic paronychial infections are common (Fig. 45). In the late stages the skin of the digits



Fig. 45. Characteristic ulcerations of finger tips in severe Raynaud's disease.

and even of the entire hand or foot may become shiny and atrophic. Sclerosis occurs in the subcutaneous tissue, forming a contracting bed of scar tissue. This results in the characteristic hidebound picture of scleroderma. This form of scleroderma is a very different process from the diffuse type which involves the face and regions other than the extremities. In such areas, as Lewis and Landis (1931) have pointed out, evidence of

a primary defect in blood flow is so slight that it cannot be regarded seriously as a cause for morbid changes in the skin.

Bone Pathology. Definite bone changes may develop in severe Raynaud's disease. Absorption of bone in the distal phalanges and the less common deposits of calcium in the soft tissues may be detected by X rays (Figs. 46 and 47).

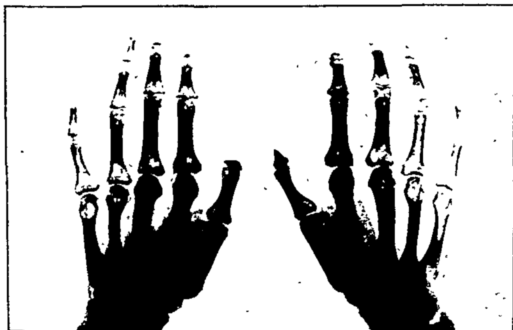


Fig. 46. Generalized decalcification and atrophy of terminal phalanges in Raynaud's disease.

Nervous System Pathology. Leriche and Fontaine (1932*B*), as well as many others, have described changes in the paravertebral sympathetic ganglia. These are characterized by narrowing of the nutrient vessels, edema of the connective tissue, lymphocytic infiltration, and degenerative changes in the ganglion cells shown by chromatolysis, vacuole formation, and abnormal pigmentation. However, Craig and Kernohan (1933), who have made a special neurohistological study of the sympathetic ganglia in 208 cases of Raynaud's disease and other allied conditions, concluded that these changes are not produced by this disease. They found identical changes in the ganglia of 40 control specimens removed from patients who had died of other conditions. The increase in pigmentation appeared to be coincident with advancing years. Similar conclusions have been reached by Dr. C. S. Kubik, who has examined the ganglia resected at the Massachusetts General Hospital.

Gagel and Watts (1932), from Foerster's clinic, reported that, on

microscopic examination of a spinal cord in a case of Raynaud's disease, they found degeneration of the sympathetic motor neuron cells in the intermediolateral cell column, but this observation has not been substantiated. As far as we are aware, there have been no reports of microscopic examination of the autonomic centers in the diencephalon.



Fig. 47. Terminal calcium deposits in Raynaud's disease.

A third area which may well be responsible for an increase in vasoconstrictor activity is the hypothalamus. Recent experimental evidence has shown that this is the central station for vasomotor control (Chap. IV), and a case of hypothalamic tumor with striking vasomotor manifestations has been reported by Peet and Kahn (1936).

ETIOLOGY

Raynaud (1862 and 1874) ascribed the cause of symmetrical dry gangrene of the fingers and toes without vascular obliteration to a sympathetic imbalance "characterized by enormous exaggeration of the excito-motor energy of the gray parts of the spinal cord which control the vasomotor innervation." This view has been held to date by the majority of writers on the subject.

On first thought, it is remarkable that Raynaud's theory of vasomotor imbalance has gone practically unchallenged for over half a century. The first investigator to question this view was Sir Thomas Lewis (1929*B*).

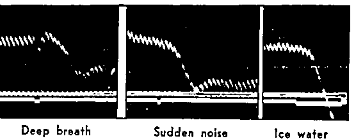
As a result of his long and critical investigation of the physiology of the peripheral vessels, he elaborated a theory of etiology diametrically opposed to that of Raynaud. He concluded that vasomotor activity in Raynaud's disease is normal, but that the peripheral spasm is due to an increased susceptibility to cold on the part of the smooth muscle in the digital arterioles. An excellent summary of his views upon this matter is given in his book which deals with vascular disorders of the limbs (Lewis, 1936). Lewis reached this conclusion from observation of the response to local cooling of the digital vessels in relatively advanced cases. He claimed that when such a stimulus is applied locally to the base of a finger a typical attack of vasospasm is induced and that it is limited to this area, whereas there is no generalized reaction on the part of the sympathetic nervous system. This reaction is hard to explain on any other basis than that of a local fault. Moreover, Lewis stated that it is impossible for the fingers to become completely blanched by a vasoconstrictor reflex, provided the hand is at rest and below the level of the heart.* He has also pointed out that if the attacks of acral syncope were due to vasoconstriction, then the entire finger should blanch simultaneously instead of the attack's creeping upward from the fingertips to the knuckles.

Two additional arguments of Lewis do not seem to us to be equally valid. In the first he assumed that procainization of the ulnar nerve at the elbow should cause complete vasomotor paralysis of the little finger. In such cases he was still able to induce well-defined vasospasm on local cooling. The flaw in this argument is that in his reported cases very little vasodilatation resulted from ulnar nerve block—in these protocols the temperature of the anesthetized fifth finger rose to only 75° F (23.5° C). In several instances of severe Raynaud's disease we have failed to secure complete vasodilatation in the fifth finger until the median as well as the ulnar nerve was blocked. This may be explained by the frequent connections between the two nerves in the forearm and hand, which may well carry some vasoconstrictor fibers. In every case of uncomplicated Raynaud's disease in which we have secured complete vasomotor paralysis, either by peripheral nerve or by paravertebral ganglion block, we have never failed to raise the digital temperature to 90° F (32° C) and thereby rendered vasospasm from local cold quite impossible.

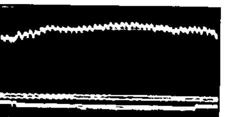
The second weak point in Lewis' interpretation is his argument that because he has succeeded in causing vasospasm by local cold after sym-

* This observation of Lewis is open to question. Simpson, Brown, and Adson (1930), who applied Lewis' tests to a series of cases of Raynaud's disease at the Mayo Clinic, stated that they observed a typical attack begin after a psychic stimulus with blanching of the fingers while the hands were at rest and below the level of the heart.

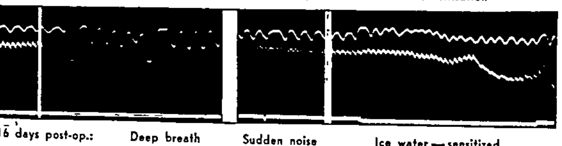
William B. 35. Raynaud's Disease.



Pre-operative: Deep breath Sudden noise Ice water



6 days after pre-ganglionic sympathectomy: Ice water — no sensitization



16 days post-op.: Deep breath Sudden noise Ice water — sensitized

Fig. 48. Vasoconstrictor reflexes before and after sympathectomy.

Variations in blood flow were detected by the photoelectric cell, which lies beneath the finger tip, through which a beam of light passes. A fall in the blood-flow level on the photograph denotes vasoconstriction; a rise, vasodilatation. The characteristic responses to various stimuli are shown. After complete sympathectomy, these are abolished. Stimuli were a deep breath, a loud noise, and immersion of the opposite hand in ice water. The reflex neurogenic responses appear within two or three seconds of the stimulus.

pathetic ganglionectomy, the condition must be due entirely to a local fault in the digital vessels. From the work of Smithwick, Freeman, and White (1934) and Freeman, Smithwick, and White (1934), we know that after this type of operation residual vasospasm in the early postoperative period may be accounted for in part on the basis of sensitivity of the denervated arteriolar muscle to adrenal secretion (see Chap. V). It is of interest that Lewis (1938*B*) found preganglionic sympathectomy more effective than ganglionectomy in relieving attacks of vasospasm. Sensitization of smooth muscle to vasoconstrictor substances also occurs after preganglionic section (Fig. 48), although it is somewhat less marked than after ganglionectomy.

In addition to these objections, it should be pointed out that Lewis based his conclusions on admittedly advanced cases, which presumably had already developed obliterative changes in the digital arterioles. He never demonstrated residual vasospasm to local cold after lumbar ganglionectomy. Furthermore, he never explained the concomitant abnormal activity of the sweat glands, which is certainly a function of an overactive sympathetic nervous system, nor the characteristic predilection for hyperemotional young women.

Great credit is due to Lewis for pointing out that changes can occur in the digital arteries fairly early in Raynaud's disease. His point that total syncope of the digits indicates a local vascular fault is well taken. Photomicrographs published by Leriche and Fontaine (1932*B*), Spurling, Jelsma, and Rogers (1932), Lewis (1938*A*), and Learmonth (see Fig. 43) prove that the digital vessels may be involved in an obliterating endarteritis. It is only his second point, that vasomotor tone is normal, which we may justly question. Keeping in mind all the facts which have been reviewed, we believe that the greatest weight of evidence is against Lewis' theory that the local fault is primary, and upholds Raynaud's original idea that at the onset of the disease the recurrent attacks of symmetrical vasospasm are due in most cases to an abnormal activity of the vasoconstrictor nerves. Any theory of the etiology of Raynaud's disease must be applicable to early as well as late cases, and equally to the hands and feet.

There is no doubt that, when local fault is present, residual attacks of vasospasm in the early postoperative period before regeneration can be a factor are more likely to occur. Also, residual vasospasm caused by sensitization phenomena is more likely to develop in patients who have local fault. Vasospasm of this sort will occur in a warm environment in response to injected adrenaline or to adrenaline secreted in response to emotiónal or insulin stimulation. Vasospasm in a warm environment due to emotional or insulin stimulation can be abolished by high spinal anesthesia.

RAYNAUD'S PHENOMENON

It is obvious from the foregoing discussion that there is a difference of opinion concerning the etiology of Raynaud's disease. It is also apparent that other conditions may manifest similar symptoms and color changes, and that the etiology is not the same in every case exhibiting these signs and symptoms. There are several possible combinations of factors which may unite to produce such an effect. It is theoretically possible for increased vasomotor impulses to act upon normal vessels and produce these changes. It is also possible for normal sympathetic activity to be present with vessels which are histologically normal, but hyperreactive, and to produce nearly the same end results. Finally, it is possible for pathological vessels, in combination with varying degrees of sympathetic activity, to produce a similar effect upon the peripheral circulation. Any of these combinations may result *in Raynaud's phenomenon. Whether sympathectomy will help, and to what* extent, can be predicted with considerable accuracy by the response to temporary interruption of vasoconstrictor impulses (Chap. VII).

II. Other Forms of Peripheral Vascular Disease Which Can Be Treated by Sympathectomy

Vasospasm Associated with Lesions in the Spinal Cord. Numerous victims of anterior poliomyelitis and occasional cases of pyramidal tract disease complain of coldness and discoloration in their paralyzed legs. These manifestations are usually of vasospastic origin and, if they respond suitably to diagnostic procaine block, can be greatly improved by sympathectomy. At one time we felt that the results of lumbar sympathectomy after infantile paralysis, when associated with extensive loss of muscular activity, were not wholly satisfactory (White, 1931). Experiences of recent years, however, indicate that the inferior results were related to inadequate (transperitoneal) denervation. Since employing the extraperitoneal approach and removing the first, as well as the second and third lumbar ganglia, the results have been satisfactory.

Thromboangiitis Obliterans and Arteriosclerosis. Numerous individuals have organic vascular disease in addition to an active vasoconstrictor mechanism. This may be confined largely to the digits, or it may be very diffuse and involve the whole extremity. Surgical intervention upon the sympathetic nervous system may be very helpful in the management of some of these patients (Smithwick, 1940*C*). While arteriosclerosis with diabetes may or may not be associated with a significant degree of vasospasm, thromboangiitis obliterans frequently has a large element of arterial spasm. In its early stages it may be impossible to distinguish this condition

from a primary vasomotor disorder. When preliminary tests indicate a favorable response, sympathectomy has been found helpful in the presence of known organic disease. We have employed sympathectomy in many cases of thromboangiitis obliterans, generally in combination with other forms of treatment such as minor amputation of digits and crushing of peripheral nerves (Smithwick and White, 1930 and 1935). In general we are impressed by the additional benefit which has followed sympathectomy in many of these patients. When, however, all main vessel pulsations including that in the femoral artery are lost, sympathectomy is less likely to be helpful, especially when ulceration, infection, or gangrene is present. The indications for peripheral nerve crushing are discussed in Chapter XXI.

Peripheral arteriosclerosis is frequently associated with enough vasomotor activity to justify interruption of sympathetic pathways. This may apply to both upper and lower extremities. Besides improvement in the circulation to the skin and subcutaneous tissue, muscular circulation may also occasionally benefit, as judged by improvement in or disappearance of intermittent claudication. This also applies to many patients with thromboangiitis obliterans. Freeman and Montgomery (1942) have performed lumbar sympathectomy in a small series of patients for relief of intermittent claudication, after first demonstrating that this symptom could be improved or was abolished by paravertebral block with procaine hydrochloride. The most frequent reason for sympathectomy in obliterative vascular disease is to increase the circulation to the skin and subcutaneous tissues of the distal portion of the extremity in order to avoid a major amputation. The relief of intermittent claudication alone is rarely the sole indication for sympathectomy. In dealing with patients having known organic disease, one must demonstrate by one method or another (Chap. VII) that the circulation can be improved before recommending sympathectomy.

Chronic Ulceration of the Extremities. Occasionally, chronic indolent ulceration in the lower third of the leg may follow deep thrombophlebitis, varicose veins, or recurrent bouts of cellulitis with abscess formation and subsequent fibrosis. When such ulcers fail to respond to ordinary methods of treatment, study may reveal a large element of vasospasm associated with the organic changes. This probably is best explained by assuming that these particular individuals have always had more than the average amount of peripheral sympathetic activity. In some cases, however, the latter may be secondary to the local lesion, particularly if pain is a significant factor. When preliminary tests are favorable, improvement has followed sympathectomy.

Frostbite may result in varying degrees of chronic vascular disease of the digits and distal portions of the extremities. When this is associated with

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pathectomy as a preliminary to ligation or endoaneurysmorrhaphy. Veal (1940) favored surgical interruption of appropriate portions of the lumbar and thoracic sympathetic trunks when a more lasting effect is desirable, and reported 3 excellent results when ligation or endoaneurysmorrhaphy was combined with lumbar or thoracic sympathectomy. Linton (1949) has recommended that sympathectomy be regularly performed prior to the excision of popliteal aneurysms. Shumacker (1947) found sympathectomy to be of value in the management of arteriovenous aneurysms, although Elkin (1946) rarely found it necessary. Deterling *et al.* (1947) have shown experimentally that sympathectomy greatly facilitates the development of collateral circulation in the presence of arteriovenous fistulas. Boyd (1946) has emphasized the value of sympathectomy in the management of traumatic false aneurysms and believes that, with its help, operation can be performed to advantage only two to four weeks after injury, rather than be postponed three to six months waiting for collaterals to develop. Boyd also obtained excellent results following ligation or excision of long sections of main arteries in 40 of 41 extremities when the procedure was combined with sympathectomy. DeBakey and Simeone (1946) were unable to show that sympathectomy was helpful in the management of a variety of acute vascular injuries in World War II, but in spite of this they were favorably inclined, in principle, to its use in these cases. In most of their cases sympathectomy was undertaken as a last resort, when amputation was almost inevitable.

It would appear that prompt elimination of vasospasm by paravertebral alcohol injection, or when possible by sympathectomy, should go far toward reducing the incidence of gangrene in cases of laceration, embolic occlusion, or ligation of major peripheral arteries. Other adjuncts such as heparin should also be employed. Murray (1940) has described how effectively this substance prevents thrombosis. It should prove invaluable in the management of various types of vascular lesions. Intermittent venous occlusion (Collens and Wilensky, 1939), passive vascular exercises (E. M. Landis and Gibbon, 1933; Herrmann and Reid, 1933; Herrmann, 1936), and the oscillating bed (Sanders, 1936) may also be used to hasten the development of collateral circulation.

An appreciation of the role of vasoconstrictor spasm in thrombophlebitis was first aroused by the report of Leriche and Kunlin (1934). DeBakey, Burch, and Ochsner (1939) have presented experimental evidence to show that reflex spasm of peripheral arteries and veins follows chemical irritation of a venous segment. The diminution of peripheral pulsations and rise of venous pressure which resulted could be prevented or abolished by interruption of sympathetic pathways. The importance of this mechanism

active vasoconstriction, circulatory difficulties ensue. Some of these patients benefit a great deal from sympathectomy. Some of the late sequelae of trench foot and immersion foot may likewise be improved by sympathectomy, particularly those related to vasospasm. Painful neuritic sequelae are less likely to be helped.

We have found sympathectomy to be helpful in the management of a few cases of thrombosis of the brachial artery with chronically impaired circulation. At times this condition is associated with a cervical rib or an anomalous first rib. Aside from pain due to compression of the brachial plexus, gangrene of the digits and intermittent claudication may also be present. Lewis (1936) feels that these complications are due to occlusion of the arterial tree by emboli. This phenomenon is usually associated with lowered surface temperature, and the main vessel oscillations may be reduced or absent. While section of the scalenus anticus muscle combined with resection of the rib back to the transverse process usually relieves the brachial neuritis, it may not improve the circulation. In several such cases gratifying improvement of the collateral circulation, with marked elevation of surface temperature, healing of ulceration, and relief of intermittent claudication, has followed preganglionic section, even when oscillations have not been significantly changed. As a rule, we have employed the anterior approach (Telford, 1935) under these circumstances.

Acute Occlusion of Major Peripheral Vessels. Following sudden occlusion of major peripheral arteries, the danger of gangrene is great. The lower extremity is more vulnerable than the upper, as the collateral circulation is inferior. In addition to mechanical interruption of main vessel flow by one cause or another, spasm of the entire vascular bed distal to the lesion may follow. If the collateral circulation fails to carry enough blood to the tissues, diffuse thrombosis will follow and gangrene will develop. Animal experiments of P. Stricker and Orban (1930), Reichert (1932), Oughterson, Harvey, and Richter (1932*A* and *B*), and Theis (1933) showed that these changes can be minimized or entirely eliminated by interruption of vasoconstrictor impulses.

Gage and Ochsner (1940) recommended early interruption of the sympathetic supply to the extremity in question by paravertebral alcohol injection. They report excellent clinical results in 10 cases in which this procedure was utilized before ligation of major peripheral arteries. Their results are most impressive and indicate that the common iliac or common femoral arteries can be ligated successfully in this way without evidence of ischemia or deficiency of the peripheral circulation. Equally impressive were the results in 4 cases of embolic occlusion of the common femoral artery. Also several peripheral aneurysms were treated by chemical sym-

therapy with foreign protein, but this form of treatment is too disagreeable, and as a rule its benefits are too short-lived to recommend it for general use. Dinitrophenol also produces a striking increase in peripheral blood flow and thereby promotes healing of digital ulcers, but this drug has proved too toxic for general therapeutic use. More recently, Reynolds and Foster (1939 and 1940) studied the effect of estrogen upon blood flow in the rabbit's ear and also upon cutaneous temperature and finger volume. No changes in surface temperature were noted. Herrmann and McGrath (1940) treated 16 patients suffering from arterial deficiency with secondary vasospasm by parenteral administration of estrogen. The results were not impressive. Our experience indicates that this substance may increase the range of motion and make the tissues more pliable when scleroderma is present. It has not prevented vasospasm in the early stages of the disease. The surface temperatures still fall to low levels on exposure to cold. Temporary improvement following Mecholyl iontophoresis was reported by Kovacs, Saylor, and Wright (1936). Perlow (1940) noted some evidence of improved circulation after subcutaneous injections and oral administration of Prostigmine. Mulinos, Shulman, and Mufson (1939) reported temporary increased circulation after intravenous injections of papaverine hydrochloride preceded or followed by histamine iontophoresis. None of these methods, however, has given sufficiently impressive results to justify continued trial.

In recent years, adrenergic blocking drugs have been developed and applied to the treatment of peripheral vascular disorders of all types. Some rather enthusiastic reports have appeared in the literature. Other observers have not been impressed by the value of these drugs. The tetraethylammonium compounds have a transient and often incomplete blocking effect and, by and large, are of little practical value. The side effects may be disturbing. Dibenamine has a more prolonged effect, but the incidence of side reactions is even greater. Priscoline has the advantage that it can be administered by mouth. However, in spite of favorable reports, it is generally ineffective in the vasospastic disorders and increasingly so as obliterative vascular disease becomes a factor.

The experience of the authors to date is that drug therapy for vascular disorders has not been effective. In addition to actual lasting results, there are theoretical objections to this approach to vascular disorders. In general, we are interested in increasing the blood supply to particular areas. Drugs which have a generalized effect upon the vascular bed are not capable of directing blood flow into a localized area. As indicated above, relaxation in vascular areas with which we are not concerned may occur, so that actually circulation in the desired area may be decreased. This is

in the production of the clinical manifestations of deep thrombophlebitis has been emphasized by Ochsner and DeBakey (1939, 1940*A* and *C*). Excellent results followed early and repeated procaine hydrochloride block of the lumbar ganglia in 20 cases. These included prompt relief of pain, reduction of swelling, and improvement in circulation. No postphlebitic sequelae such as swelling, superficial varices, or ulceration have been observed. The role of vasospasm in acute lesions involving major peripheral vessels has been summarized by Smithwick (1941).

Erythromelalgia. The condition known as erythromelalgia consists of redness and burning pain of the extremities. It may become totally incapacitating and render the patient incapable of tolerating the lightest pressure or covering of the feet. The attacks are brought on by heat, exercise, and the dependent position of the extremity. Arterial pulsations are present, and the vessels to the feet are greatly dilated. Erythromelalgia is, in many respects, the antithesis of Raynaud's disease. Weir Mitchell (1878), who first described it, considered the lesion to be a rare vasomotor neurosis of the extremities. It is known that vasodilatation in response to heating is produced by the inhibition of vasoconstriction. Following sympathectomy, the blood flow is more stable, and marked changes due to inhibition of vasoconstriction or to reflexly induced vasoconstriction are abolished. On the basis of these facts Telford and Simmons (1940) submitted 3 patients to lumbar ganglionectomy. In all of these, pain was abolished, and circulation in the feet returned to normal. The results in their first patient were followed for four years. Such cases are very rare. Our experience is limited to a single example in which a brilliant result followed bilateral lumbar sympathectomy

III. Treatment

There is no satisfactory medical treatment of Raynaud's disease. Sending the patient to a warmer climate may be sufficient for the rare individual who can afford it or can find work in the South, but even this radical change will fail to solve the problem for the severe case which fails to recover a normal circulation between attacks. Immersion of hands with normal arteries in ice water is followed by a long period of hyperemia, but Lewis (1929*B*) has shown that this response to supercooling fails in Raynaud's disease which has advanced to the stage of endarteritis. Various glandular extracts have been recommended, but there is no evidence to prove their efficacy. Roentgen therapy with the intention of influencing the vasomotor outflow from the spinal cord and dorsal ganglia has also been mentioned, but in our hands has been without the slightest effect. A. W. Allen and Smithwick (1928) reported healing ulcerations in the finger tips by fever

lumbar regions in which synapses may occur, permitting sympathetic impulses to reach the periphery even though the cervicothoracic or lumbar ganglia are removed. Thus, regardless of whether one performs a preganglionic type of sympathectomy or a ganglionectomy, it is theoretically impossible to denervate the upper extremity completely in every case. Actually, careful study of upper extremities in the early postoperative period by Robertson and Smithwick (1950) has revealed evidence of residual vasomotor activity in 14 per cent of cases denervated by preganglionic section and in 2 per cent of cases following cervicothoracic ganglionectomy. Completely denervated extremities have high skin-resistance levels (Fig. 49), reflex vasomotor and sudomotor reflexes are abolished, and cooling in response to injected adrenaline occurs.

More important, however, than any of these considerations is the question

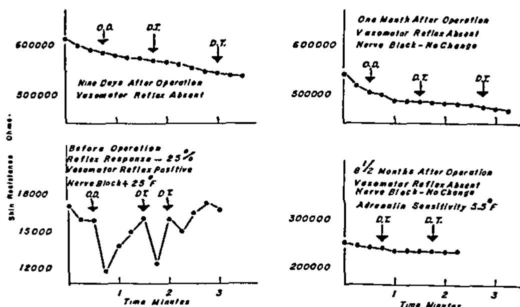


Fig. 49. Changes in skin-resistance levels and abolition of reflex response after sympathectomy.

Typical record of cutaneous resistance. Before operation the level is low and variable, and a sharp fall in response to a sudden stimulus is noted. Opening the door of the room in which the patient lay or dropping a tin on the floor was the stimulus used. After a complete sympathectomy the level of cutaneous resistance is high [illegible] that as [illegible] cause the [illegible] that this fall is due to a peripheral mechanism and is not of central origin. It may, however, be an early indication of regeneration. (Modified from Smithwick, R. H. "Surgical intervention on the sympathetic nervous system for peripheral vascular disease." *Arch. Surg.*, 1940, 40: 286–306, courtesy of American Medical Association, Chicago.)

particularly true when marked vasospasm or vascular disease exists. It is our feeling that regional sympathectomy, which directs the circulation to the area where it is most needed, is preferable to the use of generally acting, nondiscriminating, adrenergic blocking drugs. This philosophy has been ably presented by DeBakey *et al.* (1947). This whole question of the action of drugs has been discussed in further detail in Chapter V.

In general, when signs and symptoms of vascular insufficiency exist, the question of extremity sympathectomy as an adjunct to general therapeutic measures should be raised. In dealing with either a vasospastic or an obliterative disorder, it is essential to study the extremities carefully in order to determine whether or not sympathectomy will be worth while. Various methods of study are outlined in Chapter VII. When these tests are positive, one can be certain that the physiological effect of operation will be worth while. If, however, one is unable to demonstrate the presence of a significant degree of vasoconstrictor activity by any of these tests, one can be equally sure that sympathectomy will not be helpful.

IV. Results

Certain general comments may be made concerning the results of extremity sympathectomy. It is desirable to consider the effect of thoracic and lumbar sympathectomy separately. The results in vasomotor disorders and obliterative vascular disease are summarized in separate tables below.

THORACIC SYMPATHECTOMY FOR VASOMOTOR DISORDERS

The results of thoracic sympathectomy have always been inferior to those of lumbar sympathectomy. There are a number of reasons for this. First of all, the vasoconstrictor mechanism is less active in the upper extremity. Local fault is more common and may result in persistence of attacks of vasospasm following denervation by any technique. With the passage of time, sclerodermatous changes are more likely to develop in the digits of the upper extremity. This detracts from the late results Finally, incomplete sympathectomy may follow denervation of the upper extremity owing to anatomical variations in the course of the sympathetic fibers.

Ray *et al.* (1943) found evidence of the presence of sympathetic fibers in the first thoracic anterior root in 1 of 16 cases in which various roots were stimulated at laminectomy. Thompson *et al.* (1950) were able to demonstrate residual sudomotor activity following upper thoracic sympathectomy in 3 of 29 extremities in which the outflow from the first thoracic segment was not interrupted Furthermore, Skoog (1947) has called attention to the presence of ganglionic tissue along the course of the communicating rami or the peripheral nerves in the cervicothoracic and

TABLE IV

Results of Thoracic Sympathectomy for Raynaud's Disease and Allied Disorders: Clinical Evaluation

Authors	*Time Followed*	*Type of Operation*	*Number of Extremities*	*Result* Good	Fair	Poor
Haxton (1947)	1 to 14 yr	Cervicothoracic ganglionectomy	17	5	5	7
Haxton (1947)	1 to 14 yr	Preganglionic sympathectomy by ramisectomy	23	9	3	11
Barcroft and Hamilton (1948B)	1 to 6 yr	Preganglionic sympathectomy by root section	36	18	14	4
Felder, Simeone, Linton, and Welch (1949)	½ to 20 yr.	Thoracic sympathectomy (various techniques)	75	27	18	30
Smithwick, Robertson, and Farmer (1950)	1 to 15 yr	Preganglionic sympathectomy by root section	109	39	55	15
		Totals	260	98	95	67

The best clinical results have followed thoracic sympathectomy with anterior root section.

TABLE V

Results of Preganglionic Sympathectomy (Root Section) for Raynaud's Disease and Allied Disorders of Upper Extremities by Smithwick, Robertson, and Farmer (1950): Clinical Evaluation

		Complete Denervation				*Incomplete Denervation*			
Extremities Operated Upon	*Time Followed*	Number of Extremities	Good	Fair	Poor	Number of Extremities	Good	Fair	Poor
67	Less than 1 yr	53	31	22	0	14	1	10	3
55	1 to 5 yr	20	9	10	1	35	4	23	8
31	5 to 15 yr	6	3	3	0	25	11	10	4

We have included in this table only extremities which have been evaluated both physio- ... ompletely and incompletely denervated upper ... periods. The findings are very interesting: ... es are completely denervated Of these, good ... denervated cases, fair results predominate. With the passage of time the percentage of incompletely denervated cases increases steadily, so that in the five- to fifteen-year period the great majority of cases are in this category. This is due to regeneration.

It is of interest that the clinical results remain quite constant within each of the two categories for each follow-up period: Poor results are very rare in the completely denervated cases and are practically always found in the incompletely denervated category. In spite of this, the clinical results for incompletely denervated cases are surprisingly good, since the actual number of poor results is small and they are no more frequent in cases followed five to fifteen years than in cases observed for less than one year.

This table brings out the two principal difficulties which have been encountered in denervating the upper extremity. (a) incomplete denervation, and (b) regeneration.

of regeneration. With the passage of time, evidence of regeneration can be demonstrated both clinically and physiologically. The rapidity and completeness of regeneration of vasomotor fibers varies according to the technique of operation. Return of vasomotor control is most complete and rapid after preganglionic sympathectomy with ramisectomy, much less complete and delayed after preganglionic sympathectomy with intraspinal anterior root section. The results of various techniques for thoracic sympathectomy are given in Table III. It has been suggested by Felder *et al.* (1949) that if root section and ganglionectomy are combined, the late results might be

TABLE III

Results of Thoracic Sympathectomy for Raynaud's Disease and Allied Disorders: Physiological Evaluation

Authors	*Time Followed*	*Type of Operation*	*No. of Extremities*	*Physiologically Incomplete Denervation*
Haxton (1947)	1 to 14 yr	Cervicothoracic ganglionectomy	15	15
Haxton (1947)	1 to 14 yr	Preganglionic sympathectomy by ramisectomy by supraclavicular approach	31	31
Felder, Simeone, Linton, and Welch (1949)	½ to 20 yr	Thoracic sympathectomy (various techniques)	75	46
Smithwick, Robertson, and Farmer (1950)	1 to 15 yr	Preganglionic sympathectomy by root section	86	60
		Totals	207	152

Incompletely denervated extremities are rare following any technique in the immediate postoperative period. After one or more years of observation, the percentage increases. Regeneration is more complete after ramisectomy than after ganglionectomy. It is more delayed, less complete, and somewhat less frequent following root section

further improved. One of us (Smithwick) doubts that this makes much difference in the long run, since in patients observed for prolonged periods regeneration has occurred more frequently following ganglionectomy than after preganglionic sympathectomy with anterior root section. He favors the latter as the procedure of choice, to be followed later on by cervicothoracic ganglionectomy by the anterior approach if regeneration sufficient to justify a secondary procedure takes place. Simeone, on the other hand, believes that, provided root section is done along with the sympathectomy, ganglionectomy offers less chance for regeneration than leaving the ganglia in, even though they may be transplanted into muscle, wrapped in silk cylinders, or enclosed in tantalum

It is of interest that all observers have found clinical results to be much better than physiological results (Tables IV and V). The great majority of cases operated upon by the most effective technique (decentralization of

with recurrence of pain took place. The first thoracic anterior root was then sectioned, since this nerve had already been divided peripherally. Again the pain was relieved and the arm was completely denervated. Now, some six months later, evidence of regeneration is present, and the pain has recurred once more. In some cases it seems almost impossible to prevent regeneration of vasoconstrictor fibers.

LUMBAR SYMPATHECTOMY FOR VASOMOTOR DISORDERS

Vasomotor disturbances involving the lower extremity are better tolerated and are less likely to progress to ulceration, gangrene, or scleroderma. Lumbar sympathectomy is a very effective form of treatment in the experience of all observers. This is so even though the conventional operative procedures, such as removal of the second and third or first three lumbar ganglia, do not completely denervate the anterior two thirds of the thigh (see p. 31). Although regeneration may occur with the passage of time, it is more delayed in onset and less complete and frequent than in the case of the upper extremity. Consequently, both the physiological and clinical results are quite satisfactory, as indicated by Tables VI, VII, and VIII.

TABLE VI

Results of Lumbar Sympathectomy for Raynaud's Disease and Allied Disorders: Physiological Evaluation

Authors	*Time Followed*	*Number of Extremities*	*Physiologically Incomplete Denervation*
Haxton (1947)	1 to 14 yr	38	31
Felder, Simeone, Linton, and Welch (1949)	6 mo to 20 yr	30	8
Smithwick, Robertson, and Farmer (1950)	1 to 15 yr	31	9
		39	48

Evidence of incomplete denervation is not uncommon following lumbar sympathectomy. As is the case with the upper extremity, this is due more to regeneration than to an originally incomplete denervation.

TABLE VII

Results of Lumbar Sympathectomy for Raynaud's Disease and Allied Disorders: Clinical Evaluation

Authors	*Time Followed*	*Number of Extremities*	*Result* Good	Fair	Poor
Haxton (1947)	1 to 14 yr	28	16	8	4
Felder, Simeone, Linton, and Welch (1949)	6 mo to 20 yr	30	21	5	4
Smithwick, Robertson, and Farmer (1950)	1 to 15 yr	41	32	9	0
		99	69	22	8

The clinical results of lumbar sympathectomy are very satisfactory even when physiological evidence of incomplete denervation can be detected.

the upper thoracic ganglia and root section), before damage to the digits is extensive, obtain good to fair clinical results. Sympathectomy is still the best solution for the more severe vasomotor disturbances of the upper extremity, and in the opinion of the authors is much more effective than any adrenergic blocking drug which has as yet been developed.

In rare instances when there has been clear-cut regeneration of the sympathetic vasoconstrictor fibers and a return of severe and incapacitating symptoms of Raynaud's disease, we have been forced to undertake further surgery. This has consisted of resection of the cervicothoracic (stellate) and the decentralized upper two thoracic ganglia through a supraclavicular incision, or a more radical resection of these and lower ganglia with the intervening retropleural cicatrix by the transpleural route after resecting the fifth rib.

Reintervention may result in permanent clinical relief, but in several instances it has also produced severe postoperative neuralgia. It is only fair to add that pain radiating to the neck, shoulder, and upper chest has been so severe and continuous in two instances as to necessitate section of the spinothalamic tract in the medulla in order to prevent narcotic addiction (White, 1941).

In some cases secondary operations have resulted in a temporary cure to be again followed by regeneration (Smithwick, 1940*A*). In one of our earliest cases an attempt was made to interrupt regenerating fibers following a cervicothoracic ganglionectomy by excising the middle cervical ganglion. Failure of this procedure suggests that the problem of regeneration would not necessarily be solved even with inclusion of this ganglion in the original resection. This question is raised by the recent study of Kirgis, Reed, and Pearce (1950). In general it is believed that most of the synapses between pre- and postganglionic neurons for the upper extremity take place in the second thoracic, stellate, and middle cervical ganglia. It is possible that preganglionic fibers, which arise from the cord as low as the ninth or tenth thoracic segments, might have their synapses with the postganglionic neurons at lower levels. Theoretically, one might expect that if all ganglia in which synapses occur were removed, regeneration could not take place. One of our recent problem cases had a cervicothoracic ganglionectomy combined with excision of a cervical rib. The operation was performed elsewhere, and the lower root of the brachial plexus was severed during the course of the procedure Regeneration of vasoconstrictor fibers occurred and with it a severe causalgia-like syndrome involving the shoulder girdle and arm. The anterior roots of the second, third, and fourth thoracic nerves were then sectioned intraspinally, again with complete sympathetic denervation of the arm. Within a year, however, evidence of regeneration associated

with recurrence of pain took place. The first thoracic anterior root was then sectioned, since this nerve had already been divided peripherally. Again the pain was relieved and the arm was completely denervated. Now, some six months later, evidence of regeneration is present, and the pain has recurred once more. In some cases it seems almost impossible to prevent regeneration of vasoconstrictor fibers.

LUMBAR SYMPATHECTOMY FOR VASOMOTOR DISORDERS

Vasomotor disturbances involving the lower extremity are better tolerated and are less likely to progress to ulceration, gangrene, or scleroderma. Lumbar sympathectomy is a very effective form of treatment in the experience of all observers. This is so even though the conventional operative procedures, such as removal of the second and third or first three lumbar ganglia, do not completely denervate the anterior two thirds of the thigh (see p. 31). Although regeneration may occur with the passage of time, it is more delayed in onset and less complete and frequent than in the case of the upper extremity. Consequently, both the physiological and clinical results are quite satisfactory, as indicated by Tables VI, VII, and VIII.

TABLE VI

Results of Lumbar Sympathectomy for Raynaud's Disease and Allied Disorders: Physiological Evaluation

Authors	*Time Followed*	*Number of Extremities*	*Physiologically Incomplete Denervation*
Haxton (1947)	1 to 14 yr	38	31
Felder, Simeone, Linton, and Welch (1949)	6 mo to 20 yr	30	8
Smithwick, Robertson, and Farmer (1950)	1 to 15 yr	31	9
		—	—
		39	48

Evidence of incomplete denervation is not uncommon following lumbar sympathectomy. As is the case with the upper extremity, this is due more to regeneration than to an originally incomplete denervation.

TABLE VII

Results of Lumbar Sympathectomy for Raynaud's Disease and Allied Disorders: Clinical Evaluation

Authors	*Time Followed*	*Number of Extremities*	Result: Good	Fair	Poor
Haxton (1947)	1 to 14 yr	28	16	8	4
Felder, Simeone, Linton, and Welch (1949)	6 mo to 20 yr	30	21	5	4
Smithwick, Robertson, and Farmer (1950)	1 to 15 yr	41	32	9	0
		—	—	—	—
		99	69	22	8

The clinical results of lumbar sympathectomy are very satisfactory even when physiological evidence of incomplete denervation can be detected.

the upper thoracic ganglia and root section), before damage to the digits is extensive, obtain good to fair clinical results. Sympathectomy is still the best solution for the more severe vasomotor disturbances of the upper extremity, and in the opinion of the authors is much more effective than any adrenergic blocking drug which has as yet been developed.

In rare instances when there has been clear-cut regeneration of the sympathetic vasoconstrictor fibers and a return of severe and incapacitating symptoms of Raynaud's disease, we have been forced to undertake further surgery. This has consisted of resection of the cervicothoracic (stellate) and the decentralized upper two thoracic ganglia through a supraclavicular incision, or a more radical resection of these and lower ganglia with the intervening retropleural cicatrix by the transpleural route after resecting the fifth rib.

Reintervention may result in permanent clinical relief, but in several instances it has also produced severe postoperative neuralgia. It is only fair to add that pain radiating to the neck, shoulder, and upper chest has been so severe and continuous in two instances as to necessitate section of the spinothalamic tract in the medulla in order to prevent narcotic addiction (White, 1941)

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Sympathectomy should not be undertaken in the presence of rapidly advancing gangrene or infection. If ulceration or gangrene is present it must be well localized and confined to the digits or distal portion of the foot, so that sympathectomy alone or combined with a subsequent minor amputation of the transmetatarsal type will suffice. Fortunately, the advent of antibiotics has made it possible to do more closed amputations of digits and in the distal portions of the foot than was formerly the case (McKittrick *et al.*, 1949), and, as a consequence, major amputations are less frequently necessary today.

It is our feeling that the employment of sympathectomy for peripheral vascular disorders should be condemned except after careful study of the patient, as outlined in Chapter VII. Not only should this pertain to the extremities but to the patient as a whole. Extensive generalized cardiovascular disease is also a contraindication to extremity sympathectomy.

If the various methods of study are properly utilized, it is possible to predict with over 90 per cent accuracy that the result of operation will be worth while. The major consideration is to improve the circulation of the distal portion of the extremity. Obviously, this can be best accomplished before ulceration and gangrene have developed. On the other hand, many patients do not present themselves for treatment before this has occurred. Even under these circumstances, experience has shown that operation may be worth while.

In some cases the outstanding symptom which brings the patient to the doctor is intermittent claudication without ulceration or gangrene. It has been impossible to predict accurately what the effect of operation may be upon blood flow to the muscles. One can observe the effect of paravertebral procaine block upon walking ability as suggested by Freeman and Montgomery (1942) and, if the claudication is improved, one can be reasonably certain that lumbar sympathectomy will be helpful. On the other hand, we know from experience that improvement in this symptom may be delayed and may not become apparent for six months or more after sympathectomy. It therefore appears to be dubious that any acute test will ever be able to predict the precise effect of sympathectomy upon intermittent claudication in a particular patient. From a practical viewpoint the occasions for considering sympathectomy solely for the relief of intermittent claudication are rare. As a rule, ulceration, gangrene, or serious reduction in circulation to the distal portion of the extremity are much more pressing indications. Recent reports concerning the effect of lumbar sympathectomy for ulceration or gangrene and intermittent claudication are summarized in Tables IX and X. The percentage of patients

TABLE VIII

Results of Lumber Sympathectomy for Raynaud's Disease and Allied Disorders by Smithwick, Robertson, and Farmer (1950): Clinical Evaluation

		Complete Denervation				*Incomplete Denervation*			
Extremities Operated Upon	*Time Followed*	Number of Extremities	Good	Fair	Poor	Number of Extremities	Good	Fair	Poor
39	Less than 1 yr	34	22	12	0	5	4	1	0
18	1 to 5 yr	12	10	2	0	6	3	3	0
13	5 to 15 yr	10	10	0	0	3	3	0	0

In this table we have included only extremities which have been evaluated both physiologically and clinically. The clinical results of completely and incompletely denervated lower extremities are compared for various follow-up periods. The findings are very interesting, particularly in the light of those contained in Table V, which deals with the upper extremity: First of all, it is apparent that incomplete denervation in the early postoperative period is about as frequent in the lower as in the upper extremity. On the other hand, it does not detract so much from the clinical result as it does in the case of the upper extremity. It is also demonstrated that after complete denervation the clinical results are considerably better in lower than in upper extremities, since the ratio of good to fair results is much higher for lower extremities Both of these findings are most likely due to the fact that "local fault" is less frequently present in lower extremities, which are less exposed Also, vasoconstrictor tone is generally greater in the lower extremity

This table shows that regeneration is less of a problem in the lower extremity, since the percentage of incompletely denervated limbs in the later follow-up period is much smaller The clinical results are quite satisfactory for lower extremities regardless of incomplete denervation or regeneration. It should be emphasized that, in spite of these factors, both upper and lower extremities continue to be partially denervated following sympathectomy by present-day techniques, and that the persistence or later return of complete vasomotor and sudomotor control in either upper or lower extremities is extremely rare.

SYMPATHECTOMY FOR OBLITERATIVE VASCULAR DISEASE

Arteriosclerosis and thromboangiitis obliterans are the two major varieties of obliterative vascular disease, and these affect the lower extremities in particular. Rarely are the upper extremities involved sufficiently to require sympathectomy. As has already been emphasized, the results of sympathectomy in the presence of obliterative vascular disease depend largely upon the accuracy with which cases are selected for this form of treatment. The results can be very poor if no attempt at selection is made. This has been recently stressed by Yeager and Cowley (1948), who found that only 31 per cent of a series of 150 unselected cases were improved following lumbar sympathectomy for arteriosclerosis. Sympathectomy in poorly selected cases may not only be useless, but may hasten the onset of gangrene (Atlas, 1942; Freeman *et al.*, 1947). This is most likely to occur following sympathectomy for extensive obliterative vascular disease in the absence of an adequate collateral circulation. That the latter must be adequate before sympathectomy is undertaken cannot be overemphasized. It often is inadequate following sudden thrombosis of an important vessel.

Sympathectomy should not be undertaken in the presence of rapidly advancing gangrene or infection. If ulceration or gangrene is present it must be well localized and confined to the digits or distal portion of the foot, so that sympathectomy alone or combined with a subsequent minor amputation of the transmetatarsal type will suffice. Fortunately, the advent of antibiotics has made it possible to do more closed amputations of digits and in the distal portions of the foot than was formerly the case (McKittrick *et al.*, 1949), and, as a consequence, major amputations are less frequently necessary today.

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TABLE IX

Results of Lumbar Sympathectomy for Peripheral Arteriosclerosis

Authors	*Number of Extremities*	*Improved*	*Not Improved*
A. For Intermittent Claudication			
Telford and Simmons (1946)	47	47	0
de Takats, Fowler, Jordan, and Risley (1946)	19	9	10
Coller, Campbell, Harris, and Berry (1949)	31	27	4
Totals	97	83	14
B. For Ulceration or Gangrene			
Trimble, Cheney, and Moses (1944)	18	11	7
Telford and Simmons (1946)	41	21	20
Gerber, McCune, and Eastman (1949)	19	14	5
Coller, Campbell, Harris, and Berry (1949)	80	51	29
DeBakey, Creech, and Woodhall (1950)	83	29	54
Totals	241	126	115

The number of patients experiencing slight improvement in walking ability is surprisingly high, but in only some 15 per cent is the result dramatic About 50 per cent of patients with ulceration or gangrene were improved.

TABLE X

Results of Lumbar Sympathectomy for Thromboangiitis Obliterans

Authors	*Number of Extremities*	*Improved*	*Not Improved*
A. For Intermittent Claudication			
Trimble, Cheney, and Moses (1944)	15	15	0
Hamlin, Warren, and Kennard (1949)	25	15	10
Totals	40	30	10
B. For Impaired Circulation with or without Intermittent Claudication, Ulceration or Gangrene			
Trimble, Cheney, and Moses (1944)	6	5	1
de Takats (1944)	50	37	13
Hamlin, Warren, and Kennard (1949)	30	26	4
Campbell, Harris, and Coller (1949)	38	27	11
Totals	124	95	29

The results of sympathectomy in the presence of thromboangiitis obliterans are similar to those for arteriosclerosis In both groups the results can be improved by more careful selection of cases

noticing some improvement in walking ability is surprisingly high. It should be emphasized that the improvement is slight in most cases and is marked in only about 15 per cent, but statistics indicate at least some improvement experienced by the majority.

There is no doubt that a great deal can be accomplished in the treatment of obliterative vascular disease today by comparison with what

could be done twenty-five years ago. Combined therapy, proper and foot care, postural exercises, elimination of tobacco, sym tomy in carefully selected cases, antibiotics, and minor amputatio together greatly reduced the number of major amputations. Sympatl is but a single factor in the management of obliterative vascular but it is nevertheless a most important one.

V. Hyperhidrosis of Nervous Origin

The sweat glands, like the arteries, are under nervous control.] Peet (1938*A*, *B*, and *C*) have shown that these structures respond thermal and to psychic stimuli. Sudomotor, like vasomotor, activ become excessive in certain psychosomatic states. No specific factor is known for hyperhidrosis of nervous origin, but it is brougl by hyperactivity of the sympathetic nervous system which is prol hypothalamic origin. Just as generalized sweating is frequently high-strung thoroughbred horses in the paddock before a race, in beings the more localized variety of nervous sweating can be bro by any difficult mental problem or embarrassing situation. W normal individual is terrified and breaks out in a cold sweat, i hands and feet that are most strikingly involved. This is in contra generalized sweating that occurs on exposure to a hot environment. (1937) has emphasized the point that the secretory function of th is to provide an adhesive surface and to improve the grip, there viding "a teleologic rationalization of the frequently observed as of palmar sweating with certain aspects of adaptive behavior." palmar sweating represents one of the homeostatic mechanisms of tion for activity. It disappears in sleep, when autonomic activity is and differs from heat sweating, in which the palmar and plantar are usually dry. As Darrow has pointed out, the condition of th and feet may become really disabling in persons in whom "ant preparation or apprehension has become exaggerated into chronic

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Such clamminess of the hands and feet may be really disabling. Beads of perspiration may form on the finger tips and wet everything the patient handles. Shaking hands may become most embarrassing; as one of our patients, a lawyer, complained: "*The law is a handshaking profession* and I can't do it!" Another patient, a medical student, could not assist at operations because the sweat ran over the tops of his rubber gloves. A young woman college student had to wear white cotton gloves to all social functions and to carry a supply for frequent changes. The feet commonly perspire to a similar extent, so that the lower part of the sock or stocking is dripping wet. The feet of one of Telford's (1938) patients sweated so excessively that this letter carrier was forced to take off his boots and empty them of water several times a day. Excellent photographs of the excessive degree of sweating which may be seen in this condition are to be found in an article by Adson, Craig, and Brown (1935).

This type of hyperhidrosis is usually accompanied by some degree of vasospasm, so that the sweaty extremities are frequently cold and at times cyanotic. As patients with Raynaud's disease often have extremely moist, as well as cold, extremities, the two conditions seem to shade imperceptibly one into the other. Unlike Raynaud's disease, hyperhidrosis is frequently seen in males, but both diseases are likely to occur in young and emotionally unstable individuals.

Medical and Radiation Treatment. In handling cases of severe hyperhidrosis in the past, medical measures have not been helpful. Grimson, Lyons, Watkins, and Callaway (1950) have recently recommended the use of Banthīne. This quaternary ammonium compound (beta-diethylaminoethyl xanthine-9-carboxylate methobromide) is capable of blocking the parasympathetic division of the autonomic nervous system to the extent of reducing excessive activity of the sudomotor fibers as well as gastrointestinal motility and the volume and acidity of gastric secretion (see p 119). It can be taken in oral doses of 50 to 100 mg every six hours. Side effects, such as pupillary dilatation, dryness of the mouth, and a tendency to constipation may be mildly troublesome. While these authors have reported favorable results in 4 cases of hyperhidrosis, a single trial by one of us (R. H. S.) was so unimpressive that the patient required sympathectomy. We doubt very much that any cholinergic blocking drug can supersede sudomotor denervation, as sympathectomy is such a safe operation and its results have been so uniformly successful (see below).

It is difficult to imagine how a healthy young individual could prefer the use of repeated daily medication over a long period of years. The drug might, however, be of value for the rare individual who has undergone

such extensive sympathectomy that there is excessive sweating in the remaining areas of innervated skin. We have, for instance, seen individuals after extensive sympathetic denervation of the upper and lower extremities with so much sweating of the trunk that their underclothes are continuously damp in warm weather. Occasional doses of Banthīne during the summer hot spells might well prove a solution to this problem. Cutaneous application of antisudorific preparations, such as 5 per cent Formalin, may bring about a slight local reduction in sweating, but at the price of maceration and irritation of the skin. Radiation of the skin may cause atrophy of the glands, and it must be pushed to the point of risking a chronic dermatitis.

Surgical Treatment. As spontaneous activity of the sweat glands in response to heat and nervousness is mediated by the sympathetic nerves, it ceases almost entirely when these pathways are interrupted. Charts showing the areas of anhidrosis after various operations on the sympathetic nervous system have been published by Roth (1937), Richter and Woodruff (1945), and Richter (1947), the latter using the more sensitive method of testing increased cutaneous resistance to galvanic currents.

Braeucker (1928) stated that the sympathetic sudomotor axons to the hand run over the gray rami communicantes of the two lowest cervical and the first thoracic ganglia, but Kuntz (1927) had demonstrated that postganglionic sudomotor fibers are also given off by the second thoracic ganglion. From animal experiments Langley (1892) claimed that the preganglionic fibers leave the spinal cord in the motor roots from the fourth to the ninth thoracic segments. Changes in electrical resistance of the skin in the upper extremity have been demonstrated by Ray *et al.* (1943) on stimulating anterior spinal roots from the second to tenth thoracic ganglia in man, and in one instance a response was obtained from the first thoracic. Observations of Kuntz, Alexander, and Furcolo (1938) showed that a few higher fibers to the sweat glands in the cat's paw run in the first thoracic root, but the results of the operation reported below make it extremely unlikely that any significant number originate above the second thoracic nerve in man. The nerve supply to the sweat glands of the foot leaves the cord over the lowest thoracic and upper two lumbar nerves, and the postganglionic axons are distributed to the roots of the sciatic nerve from the fourth lumbar to third sacral ganglia. No matter how extensively the lumbar chains are resected, a minimal degree of sweating is likely to persist over the anterior thigh. While of no clinical significance, the academic interest of this phenomenon has been discussed above (p. 31).

Neurosurgical relief of extreme hyperhidrosis of the extremities was

first called to the attention of the medical profession through the reports of Kotzareff (*1920*), Braeucker (*1928*), Hesse (*1930*), Pieri (*1932A*), Leriche and Frieh (*1934*), and by Roberts (*1934*), Adson, Craig, and Brown (*1935*), and White (*1939*) in this country. A recent article describing favorable results in 23 cases has been published by Veal and Shadid (*1949*). In the Massachusetts General Hospital the operation was first performed in 1932. Standardized procedures are now available to sever the sympathetic fibers running to the upper and lower extremities. As the vasomotor and pilomotor are mixed with the sudomotor fibers, the operation diminishes vasoconstrictor tone in addition to causing a total paralysis of sweating and of pilomotor activity. In the case of the lower extremities, resection of the second and third lumbar ganglia can be counted on to stop sweating below the knees * as well as to produce a lasting vasodilatation.

In the case of the arm the sympathetic pathway may be interrupted in its postganglionic portion by cervicothoracic ganglionectomy, as proposed by Adson (*1934*). This produces a Horner's sign, which is somewhat disfiguring, particularly when the operation is done only on one side. The operation results in clinically satisfactory paralysis of the sweat glands of the thorax above the axilla. The sweat glands are cholinergic (see Chap. V). When denervated, they undergo no degenerative changes (Gurney and Bunnell, *1942*) and continue to react to acetylcholine (List and Peet, *1938C*), but this compound is too quickly destroyed in the circulating blood to be of any clinical significance. We believe preganglionic sympathectomy to be the preferable operation because it avoids oculopupillary paralysis, and there has been no evidence of troublesome regeneration as far as the sweat glands are concerned. For this reason we advocate the operation devised by Smithwick (p. 414) or the simpler resection of the second and third thoracic ganglia. This can be carried out bilaterally in one stage by the transverse oblique incisions recommended by White *et al.* (*1933*), with resection of the central ends of the second ribs.

The consistently satisfactory results of surgical intervention in hyperhidrosis are shown by the fact that in 32 cases treated by surgical denervation and 1 case by paravertebral alcohol injection, the condition has been relieved in all for periods running up to fifteen years In the first patient, treated by resection of the first and second thoracic ganglia, there was a detectable but clinically insignificant recurrence at eight years.

* Except for a narrow zone along the inner calf and medial malleolus, which is innervated by the saphenous nerve. This is a branch of the anterior femoral and, as such, derives some of its sympathetic connections from the first lumbar ganglion

The same was true of the patient treated by chemical denervation. In contrast to the results of vasomotor denervation in Raynaud's disease of the upper extremity, a return of sudomotor activity is never pronounced, and the patients themselves are glad to have a minimal return of moisture to their palms and fingers. All of our patients treated by sympathetic denervation have had clinically dry extremities since their operations.

We have had 2 patients who complained of disagreeable sweating in the armpits as well as in the palms. Both of these women stated that in spite of protective shields their blouses were constantly wet and stained. Satisfactory relief was obtained by removing the central ends of two ribs and carrying the ganglionectomy from T2 to T5.

The only postoperative complications that have been witnessed in these cases have been excessive sweating in other areas of the body. Two patients in whom perspiration was eliminated above the axillae have complained that their clothes, especially over the trunk, have been disagreeably moist in hot weather. We believe that every patient for whom this operation is proposed should be warned of this possibility and that sympathectomy for hyperhidrosis should rarely, if ever, be performed for both upper and lower extremities. In the vast majority of cases the patients can tolerate the condition in the feet. In the occasional case where the hands have been denervated and it is necessary also to denervate the feet, the resection of the lumbar trunk should be carried out below the second lumbar ganglion, removing only L3 or L3 and L4. The denervation is then restricted to the foot and ankle, so that compensatory sweating elsewhere is minimal.

A final point of academic interest is the phenomenon of "gustatory sweating." A tendency for perspiration to break out over the face and forehead has been observed in a considerable number of patients after cervicothoracic ganglionectomy or the Telford or Smithwick forms of preganglionic denervation of the upper extremity. This is described in Chapter X (see p. 249).

CHAPTER IX

Extremities: Bones, Joints, and Pain

I. Effect of Sympathectomy on Bone Growth

It is a common clinical observation in children that tuberculosis in a joint may cause increased growth of bone at the neighboring epiphyses and abnormal lengthening of the extremity. This is due to local hyperemia. On the other hand, the more diffuse hyperemia of sympathectomy does not cause an increased growth of either bone or soft tissue, at least in normal young animals. Cannon (1932) has demonstrated this by observing the growth of kittens after total extirpation of the paravertebral sympathetic ganglia from one side of the body. Similar observations following lumbar ganglionectomy have been recorded by Simon (1930) in young rabbits, and by Bisgard (1931) in kid goats.

These negative results in normal animals do not necessarily rule out the possibility of accelerating growth activity in epiphyses whose blood supply is pathologically reduced. Favorable results from lumbar ganglionectomy were first reported by R. I. Harris (1930) and by Harris and McDonald (1936) in children with residual paralysis after anterior poliomyelitis. These young cripples frequently develop a striking impairment of circulation in their paralyzed legs and a secondary retardation of growth. In their series of 46 ganglionectomies, hyperemia was maintained in 32, and in 26 of these the rate of growth increased on the side of the operation. This increased growth resulted in reducing the disparity in length up to 1 in. in the first year. In selecting these cases it is important that the subject should be young, so that a long period of growth remains; also that the paralysis should not be too great, because muscular activity is a necessary stimulus to growth. Wilson and Thompson (1939) have reviewed the different methods of leg lengthening They conclude that, when performed on a child under nine, lumbar ganglionectomy is capable of producing a maximum of 1 in. increased growth in the shortened extremity. This method of equalizing leg length is less effective than orthopedic measures for lengthening the bones of the leg directly or shortening those of the normal leg. On the other hand, improvement in circulation in the cold,

cyanotic, and at times ulcerated legs which are seen in these young cripples may be a strong argument in favor of sympathectomy.

Our experience with this operation has taught that, in the presence of definite vasospasm and when sufficient motor function remains so that the leg can be used in walking, a worth-while permanent increase in circulation can be counted on (White, 1931). This fortunately is the type of leg in which the prevention of shortening is of the greatest value. In the completely paralyzed extremity less lasting improvement of circulation can be obtained, and sympathectomy is usually contraindicated. Our personal experience with this procedure has been limited to 13 cases; 9 of these, after a sufficient period for evaluation, have been reported by Barr (1948). In 8 the rate of growth of the affected leg kept pace with or actually exceeded that of the opposite extremity. In only 1 has increased shortening been observed. These operations cause remarkably little discomfort to children, who need only be kept in bed a day or two and are usually able to leave the hospital within a week.

In the average child with retarded growth of the paralyzed leg, the discrepancy is usually reduced after operation, whereas otherwise it nearly always tends to increase. In a recent communication Barr *et al.* (1950) have compared bone growth in 23 sympathectomized children with a similar number of carefully selected control cases.* "Comparing the 0.3-centimeter average increase in discrepancy in the ganglionectomized group with the increase of 1.8 centimeters in the control group, we see that sympathectomy has apparently effected a stimulation of growth in the shorter extremity of approximately 1.5 centimeters per case." These observers found that the disparity of limb length actually decreased in 9 of the 23 or 39.1 per cent of the children who had been operated upon (to a maximum of 3.2 cm) and in only 2 or 8.7 per cent of the controls. They conclude that ". . . lumbar sympathetic ganglionectomy can be used in the treatment of minor discrepancies in limb length, but is probably best supplemented or supplanted by other methods, if the discrepancy is of any magnitude."

The following protocol illustrates the type of case suitable for sympathectomy and the result that may be obtained.

Paul P., 9, MGH U-3546. This boy was first seen in the out-patient department as a baby of two because he did not move his left leg. The tentative diagnosis was anterior poliomyelitis, and he was followed in the orthopedic clinic. In 1939 he was referred to the neurosurgical service because of progressive shortening of his partially paralyzed leg and coldness of the foot.

* Barr, J. S., Stinchfield, A. J., and Reidy, J. A. "Sympathetic ganglionectomy and limb length in poliomyelitis." *J. Bone and Joint Surg.*, 1950, 32-A: 793-802

The boy had a patchy paralysis of moderate degree involving the muscles of his left lower leg, with toe drop. With the aid of a caliper brace he walked well, but the left leg was 1¼ in. shorter than the right. In addition, his left foot was distinctly colder and bluer than the right, but it showed satisfactory vasodilatation on diagnostic procaine block.

1/7/40: Left lumbar ganglionectomy (L1 to L3).

The boy made an uneventful recovery and has maintained the striking vasodilatation of his foot and lower leg. Measurements made by teleoroentgenogram sixteen months after operation showed that growth of his left leg had accelerated. Whereas it was formerly 1¼ in. shorter than the right leg, it was then only ⅝ in. shorter.

A technical point about the operation is worthy of emphasis. This concerns the ganglia which must be removed. In the ordinary case of Raynaud's disease, where the poor circulation is limited to the foot, resection of the second and third lumbar ganglia is sufficient. But in this condition, where it is most desirable to increase circulation as high as the upper tibial and lower femoral epiphyses, it is important to carry the resection as high as the first lumbar ganglion. Studies on circulation by Fontaine, Houot, and dos Santos (1937) and also the determinations of postoperative sweating by Thompson, Brose, and Smithwick (1950) show clearly that it is necessary to remove the upper lumbar ganglion in order to secure an effective sympathetic paralysis as high as the mid-thigh.

II. Effect of Sympathectomy on the Healing of Fractures

Investigation of the effect of sympathectomy on the healing of fractures in animals does not, on the whole, favor acceleration of the reparative process (Pearse and Morton, 1931; Key and Moore, 1933; Zollinger, 1933*A*).

Periarterial sympathectomy was formerly advocated by European surgeons to stimulate bone repair and the healing of fractures. Among these may be mentioned Kappis (1923), Rubaschow (1925), Fontaine (1926), and Stropeni (1926). It is to be noted that, with the exception of Fontaine, no author reported more than 3 cases. In the latter's experience, 4 patients appear to have been definitely benefited, while in a corresponding number there was no apparent improvement. In this country Colp and Mage (1931) reported clinical healing in 8 of 10 cases of ununited fracture of the lower extremity within an average period of three weeks after this operation.

The treatment of ununited fractures by periarterial sympathectomy seems to us utterly illogical. In the first place, it is far more reasonable to treat the fracture itself by freshening the opposed surfaces and adding available calcium in the form of bone chips or a bone graft. This operation will

result in a general, as well as a local, hyperemia at least as great as that which could be produced by periarterial sympathectomy (cf. p. 458). In the second place, even in the presence of an active hyperemia, it is doubtful whether circulation can be effectively increased at the point where it is most needed—at the line of fracture. As Meyerding has pointed out in his discussion of Colp and Mage's paper, injection of the arteries in specimens of old ununited fracture shows that few large vessels penetrate through the dense layer of scar tissue which surrounds the fracture.

III. Rheumatoid Arthritis (Atrophic, Proliferative, or Chronic Arthritis)

The function of the sympathetic nervous system in normal and pathological joints is not well known. It has not been possible to measure how much control these nerves exert over the circulatory activity of the synovial membrane and the consequent changes in the rate of diffusion of synovial fluid. The effect of sympathectomy on arthritic pain is variable. From the best available evidence, articular sensation is mediated entirely through the peripheral spinal nerves.

The effect of cervicothoracic and lumbar ganglionectomy has been tested on a considerable number of patients with rheumatoid arthritis and associated vasospasm. Rowntree and Adson (1927) first advocated this procedure and claimed to have achieved freedom from pain with arrest or even retrogression of the disease. In a report of surgical results in a series of young patients with the periarticular type of arthritis, predominantly confined to the lower arm and leg, and in whom the circulatory defect responded well to release from control of the vasoconstrictor nerves, Adson (1933) stated that 70 per cent gave a favorable response. But with the exception of Flothow (1930, 5 cases), Leriche and Jung (1933, 2 cases), and Young (1936, 7 cases), few surgeons have been able to obtain satisfactory results. In addition, it is highly significant that no further follow-up reports have emanated from the Mayo Clinic after their early enthusiastic papers.

At the Massachusetts General Hospital 5 patients, who had been studied in the arthritic clinic by Dr. Walter Bauer, were operated upon prior to 1935. The results in these cases, which fulfilled the requirements laid down by Rowntree, Adson, and Hench (1930), were distinctly disappointing. The patients were grateful for the improvement in circulation and the reduction of perspiration in their cold, clammy extremities, but the course of the arthritis was not in any way modified. Indeed, in several patients the disease advanced more rapidly in the sympathectomized ex-

tremities than in the untreated control ones. These cases have made us realize that, although normal circulation is restored, the arrest or repair of chronic articular disease cannot be counted on. It is therefore logical to recommend sympathectomy on patients with rheumatoid arthritis only if superimposed vasomotor and sudomotor disturbances are a cause of serious discomfort. On this basis we have recommended upper thoracic sympathectomy in only a single case in the last fifteen years. This young woman, in addition to her rheumatoid arthritis, developed a posttraumatic pain syndrome in her right arm following a burn. There was extensive decalcification of the arm and shoulder girdle, and the osteoporotic hand was held immobilized in a splint and covered with a woolen mitten. She was referred to us from Vermont by Dr. R. M. P. Donaghy and was studied by the Arthritis and Psychiatric Clinics. Her pain, which was unbearable, failed to respond to standard medical treatment but was completely relieved for periods of several hours on numerous occasions by paravertebral procaine block. At our advice, Dr. Donaghy has recently performed an upper thoracic sympathectomy with a thoroughly successful result. This operation was advised for relief of painful osteoporosis, and we have no evidence that the patient's underlying rheumatoid arthritis was *directly benefited.*

IV. Painful Disorders of the Extremities

Painful disorders of the extremities which are discussed in this chapter include causalgia, traumatic arthritis, and the amputation stump neuralgias. In addition to disabling pain these conditions are characterized by trophic disturbances which consist of edema, glossy skin, muscular weakness, and atrophy of bone, and by disturbances in circulation and sweating. These complications may follow injuries to the nerves or trauma to peripheral joints. Attention was first directed to the painful sequelae of penetrating wounds which involve the peripheral nerves in the classic description of Weir Mitchell, Morehouse, and Keen (1864); the role of injury to the blood vessels was pointed out by Leriche and Fontaine (1935); and Albert (1936) has emphasized the closely related changes which are associated with trauma to the joints Frequently, the degree of disability and difficulty of treatment form a striking contrast to the insignificance of the primary injury. These conditions have been described, and the important contributions of the recent war summarized in articles by White (1946), Shumacker (1948), and Shumacker and Abramson (1949). Exactly why an occasional partial injury of a peripheral nerve, trauma (often slight)

to an ankle or wrist, and certain amputations should be the cause of a diffuse ascending neuralgia has never been satisfactorily explained.

In studying these patients it is confusing to find that the disturbances in circulation may be either in the nature of vasodilatation or vasoconstriction. Most frequently, there is hyperemia in the acute stage, followed by cyanosis, coolness, and excessive sweating of the extremity in the chronic stage. Usually, the uninjured extremities are involved as well, and we have gained the distinct impression that nervous, highly strung persons with cold, sweaty hands and feet are usually prone to develop these syndromes after injuries that would have no such effect on a more stable individual. Of course, any form of severe pain will cause reflex sweating and vasoconstriction, and patients who have suffered unremitting pain over long periods of time, often accompanied by one or more ill-advised surgical interventions, are likely to become nervous and psychoneurotic. When the situation becomes further complicated by a "compensation neurosis" or addiction to morphine, even a well-trained psychiatrist is often unable to decide whether the pain is functional or organic. As a result, many psychologically normal soldiers in the last war, with partial injuries of their peripheral nerves and suffering from severe causalgic pain, were regarded as "yellow" or as psychoneurotic by medical officers who had had no experience with this condition.

After interruption of the sympathetic outflow to the injured extremity the pain in true causalgia and Sudeck's atrophy is immediately relieved with a complete transformation of the erstwhile "psychoneurotic" patient. Similar dramatic benefit has been obtained in many individuals after amputation of fingers and toes who have developed diffuse spreading neuralgia associated with cold, cyanotic, sweaty extremities. Fortunately, the effect of sympathetic denervation can be readily foretold by diagnostic paravertebral injection of the upper thoracic or lumbar sympathetic ganglia, and at times repeated procaine block will be sufficient to give enduring relief.

In the first edition of this book the diagnostic value of blocking the sympathetic supply of the involved extremity with procaine was emphasized. The fact that repeated or even single injections of procaine might give effective lasting relief was then just becoming known. Excellent articles on this subject by W. K. Livingston (1938*B* and *C*) and Homans (1940) have appeared which give some striking examples of its value. We agree with them that the diagnostic value of procaine block is tremendous. It is usually best to repeat the injection on one or more occasions and also to be sure that sterile saline is not equally effective, especially when there

is a question of a functional disturbance. By repeated injections of procaine, permanent relief may often be obtained. The criteria for treatment by blocking the sympathetic outflow with procaine, which have been formulated by Dr. Homans and fully corroborated by us, are the following: (1) completeness of relief over the first period of effective sympathetic block; (2) the persistence of relief for a period of over two hours (prolonged duration indicates that repeated injections will cause further improvement); and (3) more prolonged periods of relief resulting from the second and ensuing injections.

When sympathetic block with procaine has given complete relief for only a short period of time, upper thoracic sympathectomy or resection of the second and third lumbar ganglia is reasonably sure to succeed.

Realizing our ignorance of the etiological factors that give rise to these conditions, we have difficulty in explaining why sympathectomy should be so effective. Kuntz and Saccomanno (1942), Threadgill (1947), and L. W. Freeman, Shumacker, and Radigan (1950) have reported evidence from animal experiments that accessory pain fibers from the extremities run centrally with the sympathetic pathways. Holden (1948), however, has been unable to confirm Threadgill's experimental results. Although it is well known that visceral pain is conducted over afferent fibers running with the sympathetic rami, the argument for an accessory sensory pathway from the extremities does not fit with other experimental evidence of R. M. Moore and Singleton (1933).* We are convinced that no such pathways exist in man because in a number of volunteers we have stimulated the lumbar sympathetic chains either in the course of operations under local anesthesia (White and Sweet, 1952) or by means of pull-out electrodes a day or two afterward (Simeone, discussion of paper by Freeman *et al.*, 1950). Such stimulation invariably gives rise to visceral pain with abdominal or pelvic radiation but has never spread to any part of the lower extremity, even in a patient suffering from amputation stump neuralgia. We realize that this conclusion is at variance with a recent report of Echlin (1949), who claims to have obtained clear-cut pain responses from stimulation of the lumbar chain in a patient with a postamputation phantom leg, and to have relieved the pain by sympathectomy. It is our feeling, however,

* Moore and Singleton found in animals that intra-arterial injections of sodium iodide or lactic acid were invariably painful. In the case of a viscus such as the liver, injection of the hepatic artery is no longer painful after resection of the splanchnic nerves. In the extremity, however, injection of the femoral artery is still painful after lumbar ganglionectomy but causes no sign of discomfort after the peripheral nerves or their posterior roots have been cut. Division of the femoral artery proximal to the point of injection likewise failed to reduce perception of pain There is therefore no evidence that pain of this type is transmitted centrally along fibers ascending in the arterial wall or through the chain of lumbar ganglia

that a solitary case report has little value in comparison to a carefully carried out series of observations and that the relief of phantom pain by sympathectomy is totally at variance with past experience.

Certain procedures which have been used in the past must be mentioned so that they may be condemned. These include periarterial sympathectomy, peripheral neurectomy, and posterior root section. While the former has given occasional successful results, we are convinced that it is a nonspecific procedure (see p. 458) and that just as much can be accomplished by procaine block or even the brief vasodilatation that follows intravenous injection of foreign protein or a malarial chill. Posterior rhizotomy is a mutilating procedure which has consistently failed. Little more can be said for removal of proximal sections of nerves, which has been known to be a useless procedure since the writings of Mitchell after the Civil War.

For the treatment of sensitive neuromata and painful stumps an entirely new method of treatment has recently been proposed by Ritchie Russell (1949). This consists simply of compression of the irritative end bulbs by constriction within a sphygmomanometer cuff or repeated percussion with a cushioned hammer. Early reports from England and our first attempts have been encouraging, but the method requires daily repetition by an intelligent and co-operative patient. The method is so simple and harmless that it merits a very thorough trial, but its possibilities have not yet been thoroughly evaluated.

When recourse to surgery is necessary, a single trial of resection of a palpable neuroma is justified, provided the end bulb is sensitive and the pain is relieved by injection of procaine. Under these circumstances all possible precautions should be taken to prevent its reformation by injecting the fresh end of the nerve with 20 per cent Formalin (Guttmann and Medawar, 1942), burying it in a drill hole through a phalanx or metacarpal or tarsal bone (Boldrey, 1943), or painting it with a 10 per cent solution of methyl methacrylate in acetone. When dried, this encloses the stump in a Lucite cap (Edds, 1945). All of these suggestions seem most logical, but in our experience pain has nevertheless usually recurred.

The essential point is not to subject these individuals to mutilating and useless major operations, as every failure is accompanied by a further reduction in the patient's morale. As shown below, true causalgia and pain in posttraumatic arthritis respond so well to sympathetic denervation that they are rarely a problem, provided surgical intervention is not too long delayed. The difficult problems are the sufferers from neuralgia following amputations above the wrist or ankle and the rarer instances of painful phantom limbs.

In these cases where pain can rarely, if ever, be relieved by sympathectomy, we recommend early recourse to anterolateral cordotomy. This operation, when performed on only one side for pain in the lower extremity, is a very benign and effective procedure (White *et al.*, 1951). To secure complete lasting analgesia of the arm is much more difficult. Falconer and Lindsay (1946) have reported two successful results, but we have suffered ultimate failure in our attempts to eliminate pain sensation as high as the shoulder both when the anterolateral quadrant of the cord was cut at the second cervical segment and after medullary tractotomy. There was early complete relief but late recurrence when the initial level of analgesia fell and was replaced by hypalgesia of the lower cervical dermatomes.

Resection of the postcentral gyrus (sensory areas 1 to 3 of Brodmann), proposed by de Gutiérrez Mahoney (1944) for the relief of painful phantom limb, is now known to be rarely effective (White and Sweet, 1952). One is therefore forced to consider frontal leukotomy for the rare case where severe continued pain is leading to morphine addiction and even the threat of suicide. From wide experience we have come to the opinion that extensive bilateral frontal leukotomy for pain leads to even greater psychical alteration and mental inertia than in the psychotic group of patients. Therefore, until a more selective method of eliminating mental reaction to pain is developed, we shall continue to reserve this drastic procedure for the rare case where preliminary cordotomy has failed and there is no other way of preventing addiction to morphine or the threat of suicide.

This general discussion of intractable posttraumatic pain in the extremities has been presented because these conditions have many points in common. There follows a short description of the three separate entities, accompanied by a number of brief case histories to illustrate the difficulties, as well as the successes, that are encountered in this type of surgery.

Causalgia. Mitchell, Morehouse, and Keen (1864) first described causalgia in soldiers following penetrating wounds incurred in the Civil War, and they gave one of the best descriptions ever written. They defined causalgia as a dysesthesia of the hand or foot following an injury in the region of a peripheral nerve. In intensity the pain varies from a trivial burning sensation to a state of torture. The pain is constant, and the patient often suffers severe exacerbation on the slightest physical or emotional stimulus. The sufferer is in a perpetual state of defense and may even protect the extremity from exposure to the air. The skin of the affected area undergoes characteristic changes, becoming red to cyanotic in hue. In some cases the extremity becomes scaly and dry, but more often it is cold and sweaty. With these changes there is a gradual atrophy resulting in a brawny infiltra-

tion of the subcutaneous tissue, trophic changes in the nails, and a thin, glossy, hairless epidermis. According to Pollock (1930), Charcot and Vulpian were among the first to describe these pathological changes which may accompany peripheral injuries or chronic sepsis. Babinski and Froment, from their experience with wounds in World War I, concluded that the coincident vasomotor changes arose from a reflex disturbance of the sympathetic centers.

White, Heroy, and Goodman (1948), from their personal observations on 13 wartime injuries of peripheral nerves and from the statistics of other military surgeons, found that causalgia occurs in somewhat under 5 per cent of wounds involving major nerves (Table XI). Echlin *et al.* (1949), who questioned 310 soldiers with peripheral nerve injuries, discovered that the early incidence of causalgia is much greater, as 61, or 19.6 per cent, gave a clear-cut history of this condition in the early period after their wound. All 61 had suffered the characteristic severe burning pain, which by its immediate onset, quality, and distribution was indistinguishable from the type that responds so well to sympathectomy. Of the 61, 56 were improved or free of pain by the time of their transfer to hospitals in this country. Nevertheless, as J. K. Mitchell (1895) found on re-examining some of his father's cases long after our Civil War, the pain may continue unabated over periods of years. When it does not show an early tendency to remission, relief of pain by sympathectomy is the only way to prevent complete functional loss of the extremity by fibrosis and atrophy, and also to save the individual from becoming a psychoneurotic invalid.

Causalgia most frequently involves the median and sciatic nerves. The injury to the nerve is usually a partial one, only rare examples having been reported following complete transection. The most striking feature of the wartime causalgias is the exacerbation of the symptoms that is encountered under any circumstances which activate a sympathetic discharge. Mitchell has recognized the disagreeable effect of such stimuli as the stirring music of a military band or the noise of heavy footsteps in the ward. White *et al.* (1948) have given special details on this score. Among the factors that gave rise to acute discomfort in these wounded sailors and marines were included such diverse stimuli as:

Cold, damp, or very hot weather
Cold air on the hand
Loud or unexpected noises, annoying radio programs
Jarrings of the bed
Anything exciting such as a narrow escape, a harrowing movie, stirring music, etc.

TABLE XI

Results of Sympathectomy for Causalgia

Case	Wound	Paralysis	Distribution of Pain	Time of Onset After Wounding	Hyperpathia	Trophic Changes	Temperature of Extremity	Sweating	Relation to Cold, Emotion	Neurosurgical Procedures in Addition to Sympathectomy	Result of Sympathectomy on Causalgic Pain
1. Chas R Pfc USMC	Small shell fragments L. upper arm	Median nerve (partial)	Entire hand.	Few hours	+ + +	+ + +	Cool	+ + +	+ + + + + +	Early median neurolysis overseas, without improvement	Complete relief, now plays strenuous games. Followed for 7 mos.
2 Chas M Pfc. USMC	Rifle bullet through arm above elbow Artery injured.	Median and ulnar nerves, complete at first, later spontaneous partial recovery	Entire hand.	After operation for aneurysm	+ +	+	Cold.	+ +	+ + + +	Ligation of brachial artery 2 weeks after wounding	Complete relief.* Followed 9 mos
3. Norman C Pfc USMC	Machine gun bullet passed between bones of upper forearm.	Median and radial nerves (partial).	Entire hand.	Few hours.	+ +	+ + +	Cool.	+ +	+ + 0	Previous neurolysis and partial suture of median and radial nerves with partial relief	Complete relief. Followed 3 mos
4. Fred S Pvt. USMC	Shell fragments upper arm and forearm	Median nerve (partial), ulnar nerve (complete).	Entire hand.	5 hours	+ + +	+ +	Cool	+ + +	+ + + + + +	Subsequent median neurolysis and ulnar nerve suture.	All hyperpathia cleared.* Followed 1 year.
5. John H Maj. USMC	Upper humerus fractured by shell fragment False aneurysm in axilla	Median nerve (complete), ulnar nerve (partial)	Entire hand, but most marked in ulnar area	Immediate.	+ +	+	Cold	+ +	+ + + + +	Ligation of axillary artery. Median nerve sutured later.	Complete relief. Followed 1 year.
6 Robt B Cpl. USMC	Bullet wound brachial plexus, fractured clavicle, severed subclavian artery.	Median (complete), ulnar nerve (partial), musculocutaneous and medial antebrachial cutaneous nerves (complete).	Entire hand, most severe in ulnar area.	1 week	+ + +	+ +	Cool.	0	+ + + + +	None	Complete relief. Followed 8 mos.

* See footnote on next page.

Case	Wound	Paralysis	Distribution of Pain	Time of Onset After Wounding	Hyperpathia	Trophic Changes	Temperature of Extremity	Sweating	Relation to: Cold	Relation to: Emotion	Neurosurgical Procedures in Addition to Sympathectomy	Result of Sympathectomy on Causalgic Pain
7. Nathan V Pvt. USMC	Rifle bullet through upper fore-arm with fracture of ulna.	Median nerve (partial)	Median distribution.		+ +	+ + + (median area).	Cold	+ +	+	+ +	Neurolysis median nerve without relief.	Complete relief. Followed 5 mos.
8. Harold O'S Pfc. USMC	Shell fragment wound of internal condyle of elbow.	*Ulnar nerve* (partial).	Ulnar area of hand.	Immediate.	+ +	+	Cold.	+ + +	+ +	+ +	Previous ulnar neurolysis without benefit.	Complete relief. Followed 5 mos
9 Howard W. Pfc. USMC	Bullet wound below elbow.	Median nerve (partial).	Median area of hand	Immediate.	+ +	+	Cold.	+ + +	+ +	+ +	Previous median neurolysis without improvement.	Complete relief. Followed 5 weeks.
10. Alfred D Pfc. USMC	Mortar wound median side of shoulder, axilla to mid arm.	Median nerve (partial), musculocutaneous (complete).	Median area of hand	Day after wound	+ + +	+	Cool.	+	+ +	+ + **	Block of brachial plexus without relief.	Complete relief. Followed 13 *mos.*
11. Wm. M Cpl. USMC	Phosphorus grenade fragments in lower leg.	Posterior tibial and common peroneal (partial), sural nerve (*complete*).	Entire foot and toes.	Immediate.	+ + +	+ +	Cold.	+ +	+ +	+ + ***	None.	Incomplete sympathectomy failed to relieve pain in anterior third of foot. Satisfactory improvement following *completion* of sympathetic denervation and neurolysis. Follow-up period of 12 months *
12. John B. GM 3/c	Razor slash across palm.	Median nerve paralysis at first *complete, then* partial recovery.	Median area.	6 months after wound with nerve recovery.	+ +	+	Cold.	+ +	+	+ +	Immediate median nerve suture.	Satisfactory relief * Followed 3 *mos.*
13. John McC Lt. (jg) USNR	Penetrating wound of lower thigh.	Posterior tibial (partial), and common peroneal nerves	Sole of foot, especially on medial side.	Immediate.	+ + +	+	Cool.	+	+ +	+ + +	None.	Complete relief. Followed 2 mos.

* Residual paresthesia and hyperesthesia of a different type connected with recovery of the injured sensory axons (see discussion).
** Patient 10 had such severe exacerbations of pain in his hand on swallowing anything cold that he was only able to sip warm liquids. This most unusual complaint was relieved immediately following procaine block and disappeared permanently *after preganglionic sympathectomy.*
*** Patient 11 complained of increase in his pain on urination and defecation, a feature which has previously been commented upon. This complication has been relieved by sympathectomy.

Reproduced from White, J. C., Heroy, W. W., and Goodman, E. N. "Causalgia following gunshot injuries of nerves: Role of emotional stimuli and surgical cure through interruption of diencephalic efferent discharge by sympathectomy." *Ann. Surg.,* 1948, 128, 161–183, courtesy of J. B. Lippincott Co., Philadelphia.

Children crying
Hypodermic injections into any part of the body
Arguments with other patients
Physical exertion
Defecation and urination
Drinking anything cold
Laughing

The common denominator underlying all these stimuli is the sympathetic discharge from the hypothalamus which accompanies all changes in environmental temperature or emotional disturbance. The importance of the efferent sympathetic discharge is clear cut and gives support to the theory proposed by Doupe, Cullen, and Chance (1944). In their opinion, injuries to peripheral nerves may lead to a breakdown in fiber insulation so that efferent vasoconstrictor impulses coming down the sympathetic axons may be short-circuited and set up ascending painful impulses in the somatic afferents. Nathan (1947) acknowledges that this is the most satisfactory hypothesis that has yet been proposed. Backfiring of this sort has been produced experimentally by Granit, Leksell, and Skoglund (1944), who found that stimulation of the anterior spinal roots led to detectable discharges on an oscillograph applied to the corresponding posterior root after an injury to the peripheral nerve. Evidence in favor of this hypothesis from human observation comes from Walker and Nulson's (1948) observation that stimulation of the upper thoracic sympathetic rami at operation in the course of many sympathectomies led to pain referred to the arm only in 3 individuals with causalgia.

The first successful demonstrations of the value of sympathectomy in relieving causalgic pain were the cases reported by Spurling (1930) and Kwan (1935). The almost invariable effectiveness of this procedure is illustrated in Table XII, which summarizes the vast experience of the recent war.

White, Heroy, and Goodman (1948) had uniformly excellent results in all 13 of their patients operated upon in the U.S. Naval Hospital at St. Albans; these are summarized in Table XI. The following case history is an interesting illustrative example.

Case 4. Frederick S, 19, Pfc, U.S.M.C.: Multiple wounds in the right upper and lower arm were received at Okinawa on 5/10/45 with partial median and complete ulnar paralysis His burning pain began five hours after he was wounded. Next to Case 1, this patient had the most severe causalgia of the entire series. When he was admitted to St Albans in July, the burning pain involved his entire hand. This became much worse in the cold, and quite unbearable on any psychic disturbance, so that he lay in a quiet, darkened

TABLE XII

Published Cases of Causalgia in World War II and Its Incidence after Wounds of Nerves

Authors	Cases of Causalgia Total	Cases of Causalgia Sympathectomized	Total Number of Wounds Involving Nerves	Percentage of Incidence	Result of Sympathectomy, Per Cent Excellent	Fair	Failure
Doupe, Cullen, and Chance (1944)	7	5	..	..	100	...	...
Mayfield and Devine (1945)	15	12	737	2	100	...	...
Ulmer and Mayfield (1946)	75	70	1477	5	95.7	...	...
Speigel and Milowsky (1945)	9	7	275	3 3	100	...	...
T. Rasmussen and Freedman (1946)	100	40	...	...	62.5	10	27.5
Allbritten and Maltby (1946)	67	30	...	...	93	...	7
Kirklin, Chenoweth, and Murphey (1947)	52	48	...	...	69	29	2
Shumacker (1948)	...	57	...	...	80 7	17.5	1.8
White, Heroy, and Goodman (1948)	.	13	400	3.3	100	.	...

room with his arm immobile on the bed and usually protected by moist towels. He complained particularly of the aggravating effect of loud noises, jarring of the bed, exciting movies, or any other psychic stimuli, of cold draughts of air over his hand, or cold, rainy weather. The patient stated that each night when he got quieted down and relaxed his pain largely disappeared and he was able to sleep well, but it would appear again soon after he awakened. At the time of his admission he unfortunately had a complicating infectious hepatitis, so that we did not dare submit him to general anesthesia and operation until his jaundice cleared. During this period of waiting his causalgia was relieved three times by paravertebral procaine infiltration of the upper thoracic ganglia, only to recur within a few hours on each occasion. Finally, sympathectomy was performed on 9/19/45, and his causalgia disappeared from this date.

A week later the nerves in his arm were widely exposed, and a long gap in the ulnar was repaired by transplantation and suture. In the upper arm there was a lateral neuroma of the median, which undoubtedly gave rise to the causalgic syndrome. In the forearm there were only fine adhesions to each trunk. Following ulnar suture and median neurolysis, the patient made excellent progress in nerve regeneration and he remained free of pain with a useful hand at the end of a year.

In cases of severe causalgia, wartime experience convinced us that lysis of adhesions and resection of lateral neuromas were ineffective in the relief of pain. It was best to do the sympathectomy first and to operate on the injured nerve at a later date. This is shown by the following case history.

Case 7. Nathan V., 28, Pfc., U S M.C.: A rifle bullet through the left elbow at Iwo Jima on 3/4/45 caused a slight injury to the median nerve. In this patient the area of burning pain, cutaneous trophic changes, and tapering fingers were limited to the territory of the injured nerve. For this reason a neurolysis of this nerve was performed first, but without any relief. Diagnostic procaine block and subsequent thoracic sympathectomy gave most satisfactory results.

In civilian practice few examples of typical causalgia are seen, the largest series having been reported by deTakats (1945). A common mistake has been to classify any case of persistent burning pain or dysesthesia as causalgia, without due regard to its origin from a penetrating wound or whether symptoms are increased by exposure to cold and psychic disturbances. Macfarlane (1949), for example, in his recent discussion of causalgic syndromes, has included such a wide variety of painful states as those following injuries to the cauda equina, arachnoiditis, and even the radicular pain that may follow cordotomy. He did not even insist that the pain have a burning quality, so it is no wonder that his sympathectomies failed to give consistently successful results. We recommend that the diagnosis of causalgia be limited to the classical syndrome described by Weir Mitchell and military surgeons in World War II. In such cases early sympathectomy, before the onset of crippling trophic and psychoneurotic changes have taken place, is nearly certain to give effective relief. With other varieties of burning sensation and dysesthesia it is essential that the surgeon be on his guard, as sympathectomy has much less to offer in these conditions which may accompany regeneration in peripheral nerves or follow crushing or other forms of trauma to the soft parts and joints. Some of these also can be relieved by sympathectomy, but there will be a discouraging number of failures unless the effect of the operation is carefully tested by preliminary paravertebral procaine block.

It may be said in conclusion that with typical causalgia, in which there is severe diffuse burning pain in an extremity after partial injury of a peripheral nerve, sympathetic denervation is nearly certain to give immediate and permanent relief. All of White's 13 patients operated upon in the Naval Hospital at St. Albans were freed of their complaints, most of them being followed for over a year. It is essential, however, that the operation be complete, as a single preliminary failure resulted from an anatomical peculiarity of the lumbar chain. This was recognized by the presence of residual sweating and later was corrected by secondary operation. Of equal importance, the regional sympathetic supply must be in-

terrupted to the level at which the nerve is injured. In the upper extremity the standard preganglionic operation is sufficient, as we have heard of no failures caused by partial late regeneration or the possible presence of a few fibers in the first thoracic root. This operation is preferable to cervicothoracic ganglionectomy, as the unilateral Horner's syndrome which follows resection of these ganglia is disfiguring. When the lower extremity is involved, it is best to resect the upper three lumbar ganglia for injuries to the nerves below the knee, and as high as the tenth or eleventh thoracic if the wound involves the sciatic trunk in the thigh or buttock (Mayfield and Devine, 1945).

Traumatic Arthritis (Posttraumatic Painful Osteoporosis). Sudeck (1900) first described reflex atrophy of bone as a clinical entity and pointed out that it might develop after fractures, trauma of the articulations, and simple torsion. A year later Kienböck (1901) added further cases and an accurate description of the changes seen at X ray. Leriche and Fontaine (1930*A* and 1935), who have made a special study of this condition, have demonstrated its constant association with vasomotor disorders and the effectiveness of sympathectomy in its treatment. Fontaine and Herrmann (1933), of Leriche's clinic, and Gurd (1936) have given excellent clinical descriptions of the disease. It is characterized by (1) weakness and atrophy of the muscles, (2) characteristic spotty decalcification of bone in the roentgenograms, (3) the constant coexistence of vasomotor disturbances, and (4) great pain. Very frequently no bone is broken, but the patient receives a blow or twist or penetrating wound in the region of a joint, most commonly the wrist or ankle. The immediate disability may be slight, but, in the course of a few days' immobilization, the joint becomes swollen, discolored, and intensely painful on any movement.

Shumacker and Abramson (1949) have been so impressed by the reflex circulatory alterations that they have proposed the name of "post-traumatic vasomotor disorders" as most appropriate for this condition. Why peripheral trauma should give rise to a reflex circulatory disorder of such a crippling nature in certain individuals is not known. During the early, acute phase there are signs of local vasodilatation (hyperemia and an increase of oscillations). Later, the hyperemia may disappear, or actual vasospasm may replace it. At this period the extremity becomes cyanotic on dependency, often edematous, and at times develops the glossy skin which is seen in causalgia. In the early period, the X ray shows a mottled appearance of the bones owing to local absorption of calcium. In the chronic stage there is a general loss of calcium salts, and the normal trabeculation of

the bones is lost. The osteoporosis is probably brought on by reflex changes in the vascularity of the bone, as it often appears too rapidly to be due solely to functional disuse.

This syndrome causes a complete disability which is very resistant to ordinary orthopedic measures; it may incapacitate the victim for months and end in bony ankylosis. Experience at Leriche's clinic showed that post-traumatic osteoporosis responds best to early sympathectomy, that the pain is usually relieved immediately, and the undesirable sequelae of the disease are prevented. Fontaine and Herrmann (1933) have presented 22 cases handled in this way. They concluded that cervicothoracic and lumbar ganglionectomy need be used only in the most extensive forms of the disease; that periarterial sympathectomy is usually sufficient for cases with osteoporosis in the hands and feet. A simpler and, we believe, more logical procedure is the paravertebral infiltration of the ganglia which transmit vasoconstrictor impulses to the brachial or lumbosacral plexuses. This is illustrated in the protocols of Cases 1 to 3, below. We believe this should be done as soon as the condition is recognized and that, in the way of prevention, much may be accomplished by employing Leriche's method of infiltrating the sensitive periarticular structures with procaine. Just why such a brief interruption of sympathetic reflexes should be effective is not clear, but it must be connected with the increase in blood and lymphatic flow resulting from release of vasoconstriction and active movement of the injured extremity (see Case 3). Free use of the extremity is certainly the key to successful therapy, and before this can be attained the pain must be relieved.

The most up-to-date article on this subject is the one recently written by Shumacker and Abramson (1949), who have had an unusually wide experience at a military hospital in World War II. Out of a series of 32 chemical interruptions of the sympathetic ganglia with procaine, 12 received no benefit, 13 transitory improvement, and 7 lasting good results. The therapeutic response to procaine block tended to be good in early cases and of much less value in those of long duration. The preganglionic type of sympathectomy was performed on 34 individuals. In those with evidence of excessive sympathetic activity, preliminary procaine block proved to be a reliable test. In numerous others, particularly in the group with edema or pain where the response to chemical block was uncertain, the result of sympathectomy was nevertheless often satisfactory. In this large series the improvement, on the whole, was gratifying. Other recent papers of special value on this subject are those by Tyson and Gaynor (1946), and Holden (1948).

The beneficial action of chemical block is illustrated in the first three case histories given below; the need for a more durable interruption of vasoconstrictor tone by sympathetic ganglionectomy in the others.

Case 1. Louis G., 44, MGH #304623. This patient had fractured the scaphoid bone in his left wrist five years previously. Following this accident, he complained of chronic swelling and a burning, aching pain in the wrist and hand. The bones in his wrist became decalcified. Two years before admission, the ununited bone fragments had been resected.

On admission, the left hand was cooler than the right, the hand and wrist were atrophied, markedly limited in mobility, and painful to touch or movement. On 2/14/30 a diagnostic procaine block of the left upper thoracic ganglia was performed. The fingers warmed from 74 to 94° F, and all pain disappeared. It had been planned to perform a ganglionectomy, but an iodine dermatitis necessitated a postponement of the operation. The patient was therefore discharged and, as he remained free of pain, returned to work as an expressman. The pain did not recur for five months. He then returned and was reinjected with procaine at his own request. Pain again disappeared for six months. At the end of this period pain and limitation of motion were again recurring, so the injection was repeated a third time. Since then, he has reported no further trouble.

Case 2. A similar patient with intractable pain following fracture of a carpal bone has been relieved with equal success by a single paravertebral injection of procaine administered by Dr. H. H. Faxon.

Case 3. Fay G., 74, MGH U-686381 BM. This elderly innkeeper slipped and severely bruised his right shoulder two years before admission. Following a period of acute pain in the shoulder, there was gradual onset of dysesthesia in the fingers. This progressed to the development of typical trophic changes: glossy skin and tapering stiff fingers in hyperextension with an adducted, rigid thumb. He carried the hand protected and immobile on a pillow. Dysesthesia was so pronounced that he was unable to cut his sensitive fingernails or wash away the crusted skin on his palm. X rays showed the typical picture of Sudeck's atrophy with extreme osteoporosis of the bones in the hand and forearm, which extended upward to involve the humerus and scapula as well. This hand was warm, without evidence of vasospasm or hyperhidrosis, and the pain was affected by neither exposure to cold nor psychic disturbances. Following a single procaine injection of the stellate ganglion, his dysesthesia and pain on movement disappeared. He was then able to start active and passive exercises and, with the aid of orthopedic measures and physiotherapy, was well on the road to recovery when he left the hospital. At ten months he reports no further pain, but slow progress in the recovery of his fibrotic hand despite every effort on his part to use the extremity.

Case 4. Barbara F., 16, MGH U-161712. An otherwise normal, healthy girl had noticed slowly increasing pain on movement of her left foot. Seven

months previously this had become much more severe, so that she could only walk with a limp on account of aching pain in the instep, which radiated as high as her knee. The pain was somewhat relieved by elevation, and the foot was distinctly moister and cooler than the right (temperature difference of 2 to 3° F). X ray showed a striking decalcification of the bones of the painful left foot. This patient was seen by the arthritic clinic, but no definite diagnosis could be made. There had been no old or recent trauma.

After paravertebral procaine block of the lumbar sympathetic ganglia, the temperature of the toes rose 13° F, and the patient was able to walk and bear full weight on her left foot. A resection of the first to third lumbar ganglia was performed on 5/2/40 by Dr. Edward Hamlin, Jr., since which time the girl has been able to walk freely and without pain.

Case 5. Lt. John S., 24, U.S. Naval Hospital, St. Albans. This Marine Corps officer had received a gunshot wound in the left buttock with compound fracture of the upper femur. The fracture had been plated overseas and had healed, but, owing to delay in transport from the South Pacific, his leg had been in a plaster cast so long that the joints were almost rigid. The bones of the lower leg, ankle, and foot were extremely decalcified. There were, in addition, trophic disturbances of the skin and excessive vasoconstrictor tone. Although there was no major nerve injury, there were such extreme dysesthesia and pain on movement that all efforts on the part of the patient and the physiotherapists to restore function had failed. Paravertebral lumbar block with procaine on 6/10/45 resulted in a pain-free period which lasted three days. After a second injection he was able to submit to massage and passive exercises. The reflex pain arc seemed to have been broken so that superficial dysesthesia disappeared, and he felt deep pain only when his joints were stretched. He was soon able to walk. His improvement, however, was not sufficient, as he could not tolerate intensive physiotherapy or walking over rough ground. Whenever he became fearful of falling he noticed increase in his pain. Decalcification of the bones in his leg was still pronounced. For these reasons lumbar sympathetic ganglionectomy was finally performed in April, 1946, by Dr. E. N. Goodman. He was then able to tolerate strenuous manipulation and began to walk without difficulty. Eight months later he remained entirely free of pain and was well on the road to recovery.

Case 6. Evelyn M., 37, MGH U-655847. Eighteen years before admission this energetic young woman strained her right wrist hitting a punching bag. The hand swelled and hurt for some time. Four years ago X rays taken on account of recurrent discomfort showed a fracture of the scaphoid bone, which was then resected. From then on she complained of constant pain in the wrist, most severe on the dorsum and radiating to her mid-forearm. It always got worse on excitement or in cold weather and made working as a "heel-cutter" difficult. X ray showed absence of the scaphoid, but only a slight degree of bony decalcification because she had continued to use the hand. As paravertebral procaine block gave temporary relief of her symptoms, an upper thoracic preganglionic type of sympathectomy was performed on

10/24/49. This spared her the minor deformity of a unilateral Horner's syndrome and afforded complete relief of her long-standing discomfort. Four months later she was back at work with only minimal discomfort in the carpal region, which was subsiding rapidly with use.

Case 7. This case history is reviewed on page 214, as the Sudeck's atrophy was superimposed on long-standing rheumatoid arthritis. Following temporary benefit on numerous occasions by paravertebral procaine block, an excellent result was obtained by upper thoracic sympathectomy.

As a result of these experiences it is our opinion that paravertebral procaine block is worth a trial in all cases. When it produces immediate but temporary loss of pain and vasomotor imbalance, it should be repeated on one or more occasions. Sympathetic ganglionectomy should be reserved for those cases in which conservative methods have failed.

Amputation Stump Neuralgia. In the major neuralgias after the amputation of a limb, the patient may complain of two varieties of pain: (1) steady burning, aching, or crushing sensation, and paroxysms of shooting pain in the stump itself, and (2) intensely disagreeable sensations in the phantom limb, which is flexed and immovable in a cramped position. If pain or contractures of the extremity are present before amputation, these disagreeable symptoms are often perpetuated by the phantom.

In the treatment of severe phantom pain we are convinced that sympathectomy has little to offer. We have tried paravertebral sympathetic block on numerous occasions and have seen a number of unsuccessful results of sympathectomies performed by other surgeons. Echols and Colclough (1947) have reported a painful phantom that developed despite a previous lumbar sympathectomy after they were forced to amputate the patient's leg because of progressive gangrene. A wartime case of Dr. Barnes Woodhall's (personal communication) is of particular interest. This officer had had his hand and lower forearm amputated following a missile wound with ensuing sepsis. At the time he was transferred to the Walter Reed Hospital he had a persistent phantom of his hand contracted as he last saw it prior to amputation. Superimposed on this phantom there was burning causalgic pain and dysesthesia of his forearm stump. Following diagnostic paravertebral block with procaine the latter temporarily disappeared, so an upper thoracic sympathetic ganglionectomy was performed. After this his causalgia disappeared, but there was no alteration in the disagreeable sensations connected with his phantom. An identical experience has been reported to us by E. N. Goodman (1947) from the U.S. Naval Hospital at St. Albans. The treatment of phantom pain usually requires interruption of its ascending spinal pathway or the cerebral associa-

months previously this had become much more severe, so that she could only walk with a limp on account of aching pain in the instep, which radiated as high as her knee. The pain was somewhat relieved by elevation, and the foot was distinctly moister and cooler than the right (temperature difference of 2 to 3° F). X ray showed a striking decalcification of the bones of the painful left foot. This patient was seen by the arthritic clinic, but no definite diagnosis could be made. There had been no old or recent trauma.

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exposed under local anesthesia and stimulated electrically. After division of the chain, cephalad stimulation caused severe pain, whereas distally it caused only a mild burning sensation in the phantom foot. After resection of the second to fourth lumbar ganglia, he was freed of his former phantom pain over an observation period of four months.

In Livingston's case there were several features somewhat unusual for this condition, viz., the stump was cool and wet, the pain was worse in cold weather, and it could be alleviated by applying a warm towel or drinking whiskey. In Homans' patient the stump was cool. These circumstances were definite indications for a trial of procaine block, a method which should always be employed in doubtful cases before the possible therapeutic value of sympathectomy is dismissed. No clue to the state of the peripheral circulation is given in Ellonen's or Echlin's reports. While we agree that a trial of sympathetic block with procaine is advisable, we have been unable to find any favorable responses either in local stump neuralgias * following amputation above the wrist or ankle, or in any instance of phantom pain. We have also failed in frequent trials of sympathetic stimulation in conscious patients to elicit any pain referred to the extremities (see p. 216) and therefore doubt that Echlin's observation will be frequently corroborated.

When properly followed over a period of months or years, it has been found that many patients who at first appeared to have been successfully relieved have eventually suffered recurrences. Kallio (1950), who made prolonged studies on prematurely reported favorable results of sympathectomy in phantom limb and other stump neuralgias, found that these procedures were useless in 39 cases. In 29 the early results were good, but after intervals of one to four years only 6 remained fully relieved and 1 had moderate improvement.

In certain ascending neuralgias following amputation of digits, however, sympathectomy may prove most valuable. In these cases there is usually local dysesthesia of the stump, as well as disagreeable, aching, diffuse pain, which may radiate proximally throughout the limb. This is commonly associated with vasoconstrictor and sudomotor activity, so that the hand or foot is cool, cyanotic, and sweaty. Usually, the other three extremities are also involved.

The discomfort is greatly increased by exposure to cold and damp. These individuals should be tested with regional sympathetic procaine

* In a single instance, (Case 3, Table XIII) where local pain in a mid-thigh amputation stump responded in a promising fashion to sympathetic procaine block, it recurred within a few months after lumbar sympathectomy.

tion fibers in the frontal lobe and therefore does not fall within the scope of this volume.

The same is true of the severe postamputation neuralgias of the arm and leg. The treatment of these when there has been no response to diagnostic block is taken up in detail in the monograph by White and Sweet (1952).

The following case histories are reported from the literature to show that our poor opinion of the value of sympathetic block with procaine in the major neuralgias following upper-extremity amputation and phantom pain may not necessarily be correct:

In 1932 Livingston (1938*B*) infiltrated the region of the left cervicothoracic ganglia with procaine hydrochloride in a physician with an intensely painful phantom after an upper-arm amputation. A Horner's sign developed, and the patient "reported that the individual fingers of the phantom hand began to feel warm and to relax, and for the first time in years he felt that he could move the fingers." Thereafter the pain did not recur with its previous severity, and he had a fair degree of relief for six months. A year later he returned, stating that for several months he had noticed an "increasing tension" in the phantom hand. He had just been on a hunting trip and had observed that the stump was often cold and that this had made his pain worse. Paravertebral procaine block was repeated, and again the phantom hand became warm and relaxed. "In the three years that have elapsed since this second injection there has never been a return of his original pain. The stump has remained warm and less sensitive, there is no jerking of the muscles, and he considers himself 'cured.' "

Dr. John Homans has described to us a successful result in a painful thigh amputation stump after five paravertebral injections of the lumbar sympathetic ganglia. In this case the stump was not cyanotic but was cool, and caused two types of pain an encircling band and a sense of severe contractions in the phantom toes. With each paravertebral block the symptoms became less pronounced and the ensuing interval of relief lengthened. A new injection was not undertaken until symptoms had begun to recur. Under this regime the pain-free intervals became progressively longer until, after the fifth injection, relief has been permanent.

Ellonen (1946) in Finland has claimed that in 6 out of 7 cases he was able to obtain complete relief of phantom pain by regional sympathetic denervation.

M. Scott and Wycis (1949) claim complete relief of a painful phantom following a mid-humeral traumatic amputation after diagnostic procaine block and upper thoracic sympathectomy, but have given no further details.

Echlin (1949) has recently reported a typical case of postamputation leg phantom in which paravertebral procaine block gave temporary complete relief of pain on four occasions. The lumbar sympathetic chain was then

block, with repeated trials if relief is of long duration. When clear-cut but only brief improvement is observed, upper thoracic or lumbar sympathetic ganglionectomy is likely to give lasting relief. The 8 cases summarized in Table XIII serve as illustrative examples. While the last 5 of these patients were wartime cases in which prolonged follow-up has been impossible, the first two have been followed for long periods (over twenty years in the first case). Case 3, the single patient with a proximal limb amputation, one of the few instances in which we have been misled into doing an ineffective lumbar sympathectomy because of a favorable response to paravertebral procaine block, developed recurrent pain after seven months. It is our belief that the beneficial effect of interrupting sympathetic fibers in these postamputation neuralgias is not due to interruption of pain fibers but to improvement of local circulation. Vasodilatation is pronounced in the hand or foot but minimal in amputations above the wrist or ankle.

TABLE XIII

Relief of Local Pain after Amputation by Interruption of Sympathetic Fibers

Case	*Condition*	*Surgical Procedures*	*Relief*
1. Roger P. MGH # 302151	Crush of index finger and amputation associated with cold, clammy hand; pain in hand radiating up inner arm to pectoral region.	1 Reamputation of finger . .	None
		2 Paravertebral procaine block T1–T2	Relief for 2 hrs.
		3. Cervicothoracic ganglionectomy . .	Complete relief lasting over 20 yrs
2. Roland L. BM # 879	Traumatic amputation of index finger associated with cold, sweaty hand.	1 Reamputation of finger	None.
		2. Paravertebral procaine block T1–T2 .	Transitory relief.
		3 Cervicothoracic ganglionectomy .	Permanent relief.
3. James B. MGH U-222390	Burning pain developing in stump 30 yrs. after thigh amputation; pain present for 3½ yrs	1 Section spinothalamic tract with sensory level at T12	Relief for 4½ mos with recurrence following transurethral prostatectomy.
		2 Paravertebral lumbar procaine block	Relief for 2 days.
		3. " " " "	Relief for 4 wks.
		4. " " " "	Relief at discharge.
		5. Lumbar sympathectomy L1–L3	Relief for 7 mos., then recurrence
4. Henry J. CM 3/c USN	Traumatic amputation of distal phalanges of 4th and 5th fingers. Very cold, cyanotic, sweaty hands	1. Paravertebral procaine block T1–T2 .	Temporary relief.
		2. Upper thoracic preganglionic sympathectomy	Warm hand and arm free of former deep pain at discharge (3 wks.)
5. John G. S 3/c USN	Traumatic amputation 2nd and 3rd fingers. Local hyperesthesia in 3rd finger had been relieved by excision of neuroma, but without effect on neuralgia of hand and forearm	1. Paravertebral procaine block T1–T2 ..	Temporary relief.
		2. Upper thoracic preganglionic sympathectomy	Complete relief of ascending neuralgic pain. Patient still complained of hypersensitive index finger but was able to return to limited duty.
6. Philip C. Sgt. USMC	Traumatic amputation tip of 5th finger with repeated amputations to metacarpal level for local hyperesthesia and deep ache in hand and arm. Cold, cyanotic hands.	1. Procaine block of upper thoracic ganglia	Relief for 2 hrs.
		2. Upper thoracic preganglionic sympathectomy	Nearly complete relief of deep aching pain in hand and arm at 3 mos.
7. Henry C. S 2/c USN	Traumatic amputation of 3rd toe, with severe pain in stump and bottom of foot. *Aggravated by cold, not by psychic stimuli.*	1. Paravertebral procaine block	Temporary relief.
		2. Lumbar sympathectomy L2–L3	Complete relief at 2 mos.
8. James L. AB R.N	Traumatic metatarsal amputation with painful vasospasm. Deep ache in end of foot, which became much worse in cold weather and ascended to knee.	1. Paravertebral procaine block	Temporary relief.
		2. Lumbar sympathectomy L2–L3	Excellent result.

The Naval and Marine Corps patients were operated upon at the U.S. Naval Hospital at St. Albans, N.Y.
The statistics in this table have already appeared in the *American Journal of Surgery* (White, 1946), courtesy of the editor.

extrasystoles, changes in the shape of the T waves, and complete inversion of the electrical axis of the heart. It is also of interest that the irritability of the carotid sinus is increased by digitalis, morphine, and thyroid extract.

The possibility of a latent hyperirritable sinus should be borne in mind by every anesthetist and surgeon who operates in this portion of the neck, especially in arteriosclerotic individuals. In freeing the upper pole of the thyroid and in resecting cervical glands, this sensitive area is necessarily traumatized and may thereby produce sudden reflex collapse of the patient. Cardiovascular or respiratory collapse of this sort can usually be combated by procaine infiltration or by deepening the anesthesia to depress reflex irritability. Weese (1939) has called attention to the important fact that fatalities may occur during operation upon abscesses in the neck under barbiturate, light ether, or nitrous oxide anesthesia. The anesthetic management of such complications has been well described by Rovenstine and Cullen (1939) and Ruzicka and Eversole (1942). The explanation of severe reactions in these cases is the increase in carotid sinus irritability secondary to inflammatory processes or arteriosclerotic changes. In order to avoid alarming and sometimes fatal collapse in the course of operations on the neck, sensitivity of the sinus should be tested by compression in all older persons and, if it is found irritable, deep ether anesthesia should invariably be used, as this depresses sinus irritability. When alarming signs develop, such as pallor, apnea, hypotension, or slowing or irregularity of the heart, treatment must be instituted without delay. The head of the table should be lowered, sponges and retractors removed from the incision, and 2 per cent solution of procaine infiltrated around and between the carotid bifurcation.

It is of equal importance that the possibility of an irritable sinus should be kept in mind and excluded by the neurologist in the routine examination of every patient who suffers from convulsive seizures, and by the cardiologist in older individuals who suffer from attacks of heart block and other cardiac irregularities.

In asystole or reflex slowing of the heart, the efferent arc of this reflex is over the vagus and therefore can be abolished by atropine. The second type of response, which is characterized by a fall in blood pressure, can sometimes be benefited by ephedrine, but the primary attacks of syncope and convulsions can only be treated by denervation of the sensitive sinus.

In selecting patients for operation, infiltration of the sinus with procaine should be carried out as a diagnostic test, according to the technique described by Pick and Wertheim (see p. 464). Great care must be used not to inject the solution into any of the large blood vessels. The production

CHAPTER X

Head, Brain, Meninges, and Spinal Cord

Carotid Sinus Syndrome. Weiss and Baker (1933) have drawn attention to an unusual syndrome of recurrent attacks of syncope due to an overactive carotid sinus reflex. The investigations of this vasodepressor mechanism by Professor Heymans and his associates in Ghent have been reviewed in Chapter IV (see p. 75). The carotid sinus plexus (Fig. 16), which originates at the bifurcation of the carotid artery and sends filaments to the glossopharyngeal, vagus, and cervical sympathetic nerves, causes a generalized vasodilator response when the blood pressure rises in the carotid bulb The glossopharyngeal nerve carries the important afferent impulses of the reflex arc to the vagal center in the medulla (Ray and Stewart, 1942). Whereas in normal subjects mechanical stimulation of the sinus causes a fall in systemic pressure of less than 10 mm, the exaggerated drop in the presence of an abnormally sensitive sinus may cause spontaneous fainting attacks and, at times, convulsions. In Weiss and Baker's cases digital pressure on the hypersensitive carotid sinus promptly induced symptoms identical in every respect with the spontaneous attacks. This abnormal response is either entirely unilateral or much more marked on one side than on the other.

Three types of carotid sinus reflex have been described: (1) asystole or sudden slowing of the pulse with or without fall in arterial pressure, (2) marked fall in blood pressure without pronounced slowing of the heart, and (3) changes in the cerebral circulation, causing fainting and at times convulsions, with or without striking alteration in the heart rate or blood pressure.

While the syndrome of the hyperirritable carotid sinus is not difficult to diagnose in its characteristic, fully developed form, this is far from being the case with its less common manifestations. The hyperactive reflex can induce striking changes in the intracardiac conduction system. In addition to complete heart block, these include temporary asystoles of the ventricle with continued auricular contraction, nodal rhythm, ventricular

mild degree of arteriosclerosis, and his neurological examination was not remarkable. Lumbar puncture showed an initial pressure of 200 mm, but no other abnormalities. X rays were taken to rule out cervical rib and changes in the skull.

On testing the carotid sinus reflex by digital compression, it was found that pressure on the right caused a fall in blood pressure from 140/70 to 60/? mm. The pulse rate fell from 100 to 60, but there were no other significant changes in the electrocardiogram. Pressure for fifteen seconds caused deep flushing of the face, followed by the symptoms he had complained of in his left arm; when the pressure was maintained for twenty seconds he lost consciousness and had a mild left-sided convulsion. Pressure over the left carotid sinus produced a similar depression of the pulse rate and blood pressure, but much less marked symptoms. After procainization of the sinus on the right, pressure sufficient to occlude the artery could be maintained for a long time without discomfort or any detectable vascular reflex.

The patient was seen in consultation by Dr. R. B. Capps of Dr. Soma Weiss' Service of the Boston City Hospital. He felt that the case was a typical instance of the carotid sinus syndrome with a predominating cerebrovascular reflex. Operation performed on 11/28/34 showed a distinct enlargement of the carotid bifurcation. On handling what appeared to be a group of nerve fibers which lay between the two carotid branches, the patient's blood pressure dropped to 60 mm. Procaine infiltrated into this area caused an immediate rise to his normal pressure and prevented any further fluctuation. The bifurcation of the common carotid artery as well as the lowest 2 cm of its external and internal carotid branches were carefully denuded of all strands of nerve and connective tissue in their adventitial layer (see Fig. 96).

Recovery from this operation was uneventful, and the patient left the hospital six days later. At that time he was completely relieved of his previous symptoms of weakness and fainting. When re-examined two years later, the patient stated that he was well pleased with the result of the operation and had had no more of his old seizures. Pressure over the carotid bifurcation could be carried out with impunity.

John C., 69, MGH U-241410. Arteriosclerosis and bilateral carotid sinus syndrome with bradycardia, hypotension, and petit mal seizures.

A healthy truck driver started to have "fainting spells" in January, 1940. These came on without warning up to ten times a day and forced him to give up his work. The spells consisted of sudden arrest of purposeful activity without loss of consciousness or convulsive movements. He would suddenly stop whatever he was doing, swallow several times, and appear somewhat cyanotic and distressed. Such attacks lasted fifteen to forty seconds. There was no past history of epileptic seizures, head injury, or encephalitis, nor were there any symptoms or signs suggestive of brain tumor.

Both carotid arteries were unusually prominent, dilated in the region of their bifurcation, and contained flecks of calcium in their walls. A typical seizure could be induced from massage of the sinus region on either side, but more easily on the left. His blood pressure was 190/90.

of a Horner's sign or recurrent laryngeal nerve paralysis indicates a thorough infiltration of the tissues around the carotid sheath. Under these circumstances all symptoms due to a carotid sinus reflex should be abolished, and operative resection of the sinus nerves can be counted on to give a corresponding degree of lasting benefit.

Operation may be performed under the same local anesthetic or supplemented with ether. In any event, abolition of the reflex irritability of the sinus with procaine is an added safety factor, because severe disturbances set off by the trauma of dissection are thus eliminated. Numerous reports of carotid sinus denervation for syncope and convulsions are now on record and show very satisfactory results: Weiss, Capps, Ferris, and Munro (1936) have reported 10 cases, with lasting relief of seizures in 8; 4 further cases have been described by Freedburg and Sloan (1937) and 3 by Cattell and Welch (1947). In cases described by Romano, Stead, and Taylor (1940) and by Rabwin and Merliss (1950), abnormal brain waves, which made their appearance on stimulation of the irritable sinus, disappeared after surgical denervation. Even bilateral denervation of the sinus is not dangerous, according to R. B. Capps and de Takats (1938) and Craig and Smith (1939). Postoperatively, 2 of the patients reported by Capps and de Takats showed a significant postural hypotension, but no elevation in blood pressure or heart rate has been observed after removing these important reflex mechanisms for cardiovascular control. We have now denervated irritable carotid sinuses in 4 patients, twice bilaterally. All of these individuals suffered from sudden syncope and convulsions. The results were uniformly satisfactory, although in Case 3, after a unilateral denervation, the syndrome appeared on the opposite side, requiring a second operation.

The following three cases illustrate some of the interesting features of this condition:

Socrates G., 62, MGH #16290 BM. Arteriosclerosis and carotid sinus syndrome with bradycardia, hypotension, and left-sided convulsions.

The patient had been in good general health until three years before admission. He then noticed a gradual onset of transient spells of weakness and faintness. These were frequently induced by turning his head to the left or by bending his neck backward, they occurred on the average of two to three times a day. He would have to brace himself to prevent falling, and had actually fallen down on a number of occasions. Associated with the general weakness, he noticed awkwardness and heaviness in his left arm and leg, with occasional twitchings in the left side of his body. Frequently, the attacks gave him a dreaded sense of imminent death

The general examination of the patient revealed nothing abnormal beyond a

mild degree of arteriosclerosis, and his neurological examination was not remarkable. Lumbar puncture showed an initial pressure of 200 mm, but no other abnormalities. X rays were taken to rule out cervical rib and changes in the skull.

On testing the carotid sinus reflex by digital compression, it was found that pressure on the right caused a fall in blood pressure from 140/70 to 60/? mm. The pulse rate fell from 100 to 60, but there were no other significant changes in the electrocardiogram. Pressure for fifteen seconds caused deep flushing of the face, followed by the symptoms he had complained of in his left arm; when the pressure was maintained for twenty seconds he lost consciousness and had a mild left-sided convulsion. Pressure over the left carotid sinus produced a similar depression of the pulse rate and blood pressure, but much less marked symptoms. After procainization of the sinus on the right, pressure sufficient to occlude the artery could be maintained for a long time without discomfort or any detectable vascular reflex.

The patient was seen in consultation by Dr. R. B. Capps of Dr. Soma Weiss' Service of the Boston City Hospital. He felt that the case was a typical instance of the carotid sinus syndrome with a predominating cerebrovascular reflex. Operation performed on 11/28/34 showed a distinct enlargement of the carotid bifurcation. On handling what appeared to be a group of nerve fibers which lay between the two carotid branches, the patient's blood pressure dropped to 60 mm. Procaine infiltrated into this area caused an immediate rise to his normal pressure and prevented any further fluctuation. The bifurcation of the common carotid artery as well as the lowest 2 cm of its external and internal carotid branches were carefully denuded of all strands of nerve and connective tissue in their adventitial layer (see Fig. 96).

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Studies were undertaken in Dr. R. S. Schwab's laboratory, making simultaneous records with the electrocardiogram and the electroencephalogram during massage of the irritable sinuses. The cardiac tracing showed periods of asystole up to 3.5 sec, while the brain potential record revealed occasional slow waves (5 per second), followed by a marked drop in voltage. Pressure on the right sinus produced identical, but less striking, abnormalities.

Decortication of the common, external, and internal carotid arteries for a distance of 2 cm above and below the bifurcation on the left side was carried out on 8/19/40, with a particular effort to obtain a clean resection of the nerve structures at the region of the sinus itself. In order to do this the ascending pharyngeal artery was ligated and cut, as it originated from this area along with numerous nerve fibers in a network of fibrous tissue. The adventitial stripping was rendered difficult by the plaques of calcium in the carotid bulb, but was nevertheless carried out thoroughly over this area.

The patient recovered uneventfully. When tested two weeks after operation, pressure on the left sinus no longer induced changes in the electrocardiographic or electroencephalographic tracings. Right-sided pressure still caused characteristic objective and subjective effects.

Four months later similar tests showed that the sinus on the left remained unresponsive. Instead of a great many troublesome seizures, the attacks continued to be milder and more infrequent, averaging three per day. These could be induced by gentle massage over the right carotid sinus. Accordingly, on 1/9/41 the sensitive zone at the right carotid bifurcation was denervated by dissecting the adventitia and nerve filaments from the junction of the common, external, and internal carotid arteries. Convalescence was uneventful. We were particularly interested to see if denervation of both carotid sinuses, with the consequent loss of vasodepressor reflexes, would bring about any rise in blood pressure. No such response could be detected, and it must be concluded that there are other reflex regulatory centers which are capable of maintaining a normal vascular tone in man. The patient was discharged from the hospital six days later without having noticed any recurrence of his attacks.

When seen two months afterward he had noticed no spells, but his wife thought he had had a few minor seizures in his sleep. Pressure over the carotid bifurcation failed to elicit any form of sinus reflex from either side or to change the normal wave pattern of the electroencephalogram and electrocardiogram.

Mary W., 44, MGH U-364456. When this middle-aged woman was first admitted to the Neurological Service in 1942 because of frequent major seizures, a diagnosis of hyperostosis frontalis interna was made. As no cerebral focus could be located by clinical examination, electroencephalogram, or pneumography, she was discharged on anticonvulsant medication. As she continued to have generalized seizures and observed that one of these occurred when her head was turned far to the left, carotid sinus compression was tested. On left-sided stimulation she exhibited a typical attack. She had a premonitory sensation of blood rushing to her head with a pounding headache and was

then unable to talk. This was followed by loss of consciousness, with adversive turning of the head and eyes, frothing at the mouth, and then purposeless movements of the arms and legs. The pulse slowed to 60, and blood pressure fell from 120/80 to 86/40. The electroencephalogram showed the appearance of 5- to 6-per-second waves and disappearance of normal rhythm over a corresponding period.

Following left-sided denervation on 10/2/42, she was completely freed of her seizures for several months. She got along well on Dilantin medication for the next five years, but slowly developed evidence of increasing irritability of the sinus on the right. Denervation was carried out on 7/28/48. When tested thereafter with simultaneous electroencephalographic and electrocardiographic recording, no evidence of residual sinus irritability could be detected on either side. She was examined ten months later and found symptom free.

One further patient, an arteriosclerotic hypertensive woman of 63, had complete relief of asystole following denervation of the irritable left carotid sinus, but after three months the previous minor seizures recurred. At this time the carotid sinus compression test showed no abnormal irritability on either side, and the electroencephalogram remained unchanged. It was concluded that her spells were due to cerebral ischemia on an arteriosclerotic basis.

Epilepsy. Penfield (1933) has stated that "the one constant visible phenomenon in the brain during an epileptic seizure is cessation of arterial pulsation. The epileptic brain is subject to local vasomotor reflexes such as have never been described in the normal brain." Although active vasomotor control of the cerebral blood vessels is an established fact, it is most unlikely that any such localized response should be mediated by the cervical sympathetic outflow. This focal constriction of cerebral vessels must probably be due to local lesions (Cobb, 1938). As a rule it cannot be prevented by interruption of the cervical sympathetic trunks, but frequently it may be corrected by excision of irritable areas in the cerebral cortex. Measurements of blood flow in the jugular vein made by Gibbs, Lennox, and Gibbs (1934) before, during, and after epileptic convulsions have shown that there is no widespread ischemia of the brain preceding or during an attack.

The first recorded sympathectomy was performed by W. Alexander (1889) of Liverpool for the relief of epilepsy. This operation was carried out on a fairly large number of epileptics by Jonnesco (1896) and other surgeons without striking success. Further anatomical investigation showed that Jonnesco's operation left the sympathetic rami along the vertebral artery intact, so that the cerebral vessels were only partly cut off from their vasoconstrictor nerves (Fig. 15). Consideration of these facts led Mixter

and White to attempt total sympathetic denervation of the brain by bilateral cervicothoracic ganglionectomy. This was carried out in a series of 17 patients suffering from frequent and severe epileptic attacks. Every case had been subjected to a careful preoperative study by the neurological service, with encephalograms in most instances to rule out localized injury to the brain cortex. None had responded to ketogenic diet or to phenobarbital. These were reported in the 1935 edition of this book, prior to the discovery of Dilantin and the other newer and more efficient anticonvulsant drugs. At the time of its publication, results in 3 of 17 cases were encouraging. But it was pointed out that the period of follow-up was short and that, in the past, other entirely nonspecific operations, such as colectomy, had produced a number of apparently successful temporary results. This conservative attitude was not ill founded, as the final outcome in these 3 cases has been disappointing. We therefore believe that complete sympathetic denervation of the brain has been given an adequate trial and found to be without benefit in the convulsive state.

Migraine. As W. Harris (1936) has pointed out, it can scarcely be doubted that typical ophthalmic migraine, which is preceded by sudden disturbances in one of the visual fields and other cortical disturbances, must be associated with vasomotor changes in the cerebral vessels, while the succeeding stage of headache is associated with vasodilatation of the middle meningeal, temporal, and other branches of the external carotid artery. D. Clark, Hough, and Wolff (1936) have demonstrated that this is the mechanism of experimental headaches induced by intravenous injection of histamine and that the pain is caused by stretching of the perivascular plexus of sensory nerves. Nevertheless, there is no evidence to indicate that either this vasodilator response or its sensory conduction are carried over the cervical sympathetic trunks. We have observed the effect of unilateral cervicothoracic ganglionectomy and of procaine block of these structures on the headaches produced by histamine, lumbar puncture, and pneumoencephalography and have been able to find no evidence that pain is reduced on the denervated side. Furthermore Solomon (1936) was unable to demonstrate any general sympathetic disturbance during the evolution of a migrainous headache by such a delicate test as measurement of the electrical resistance of the skin, nor was there any change when the headache was relieved by ergotamine.

It must, however, be admitted that there is some older evidence that migraine and other forms of headache may be relieved by sympathectomy, but the reports are too few to be convincing. Love and Adson (1936) studied their patients who had been submitted to cervical or cervicothoracic

sympathectomies for conditions other than headache, but who complained of headache in addition to their primary disease. They were able to follow 16 patients, of whom 12 were either partly or completely relieved and 4 were unaffected. Dandy (1931) and Craig (1935) have each reported 2 cases of severe hemicrania relieved by cervicothoracic ganglionectomy. But if this operation were consistently effective there should be a larger number of enthusiastic case reports. We have tested a number of patients by diagnostic injection of procaine during their attacks. They have developed satisfactory signs of sympathetic paralysis, but without benefit to their headaches—in one patient the headache became definitely more severe.

A most valuable description of the sensory innervation of the dura mater has been written by Penfield and McNaughton (1940) which gives the first satisfactory explanation of the propagation of migrainous headache. These investigators have studied the nerve supply of the dura mater in cleared preparations. Their findings in brief are as follows:

The dura is in large part insensitive, but it contains sensitive areas which coincide with the meningeal vessels and the large venous sinuses.

Stimulation of the middle meningeal artery causes pain which is localized by the patient near the point stimulated. This is transmitted by filaments from the second and third divisions of the trigeminal nerve.

The ache which results from stimulation of the longitudinal and straight sinuses is referred to the forehead and eye, because the innervation of these structures is received from the ophthalmic or first division of the trigeminal nerve.

Stimulation of the sigmoid sinuses and region of the jugular bulb is referred to the region of the mastoid and transmitted over the vagus.

When these observations are coupled with the findings of Clark, Hough, and Wolff (1936) that headache is due to excessive pulsation and stretching of the walls of the dural and temporal arteries, the only reason for supposing that cervical sympathectomy can be of value is the assumption that it causes a reduction of the vasodilator response. There is little evidence to favor this assumption. A far more logical procedure has been proposed by Penfield (1932) and further recommended by W. Harris (1936) and by Penfield and McNaughton (1940). This consists of selective section of the upper and medial fibers of the trigeminal posterior root. This interrupts the sensory fibers to the blood vessels of the dura and scalp, which have been shown by Clark, Hough, and Wolff (1936) to play such an important role in these headaches. Its effectiveness has been shown in a recent experience of one of us (J. C. W.). In this patient, a drug addict

because of the severity and frequency of her hemicrania, previous section of the external carotid and middle meningeal arteries had been tried without benefit; division of the great superficial petrosal nerve, as recommended by Gardner *et al.* (1947), had also been ineffective.

In conclusion, it can be stated that available evidence suggests that the autonomic nervous system is implicated in the abnormal pulsations of the cranial branches of the carotid artery which are so important in migrainous headache. But there is little evidence that these impulses ascend in the cervical sympathetic trunk nor to show that afferent impulses traverse this route (see below). When confronted with cases of intractable migraine, a trial of cutting the temporal and middle meningeal arteries is recommended as a preliminary procedure, to be followed by section of the upper and medial two thirds of the trigeminal root if the minor procedure is unsuccessful. Since the section of the root is performed through the same opening made to expose the middle meningeal artery, there is little to be lost by postponing this to a second stage, if it is necessary.

Atypical Neuralgias of the Head. Trigeminal and glossopharyngeal neuralgias are two very characteristic syndromes. Patients submitting to rhizotomy after accurate diagnosis are consistently relieved. The sphenopalatine neuralgia described by Sluder (1918) is a less definite entity, but pain is referred to the region behind the nose and eye, and at times spreads over the entire side of the head and neck. It can be diagnosed by the relief which follows infiltration of the ganglion with procaine. These forms of neuralgia constitute distinct entities and can be relieved by standardized surgical procedures

In contrast to the classical varieties of neuralgia, atypical forms are extremely difficult to diagnose and to treat. The pain may involve the area of the trigeminal nerve, but it is more constant and may even become continuous It is described as a deeply seated, burning, throbbing, aching pain, which is not limited to the distribution of the fifth cranial nerve but may involve one entire side of the head and neck. At times even the shoulder and arm become involved. Frequently, the great vessels in the neck become extremely tender to palpation. Although the patient does not suffer as excruciating pain at any one moment as the typical case of tic douloureux, yet the constant, unremitting nature of the condition is a cause of real torture. Tinel (1930) has described a patient with this condition which developed following an accident eight months after total resection of the trigeminal root for tic douloureux. Postoperatively, the patient had developed a facial palsy, but in spite of the complete paralysis of the fifth and seventh cranial nerves, she continued to suffer. This pain

was more severe, but different in character and distribution, radiating over the entire left half of the head and neck.

Largely because no other afferent pathway was known, it was formerly believed that some pain fibers from the face and head might run over the cervical sympathetic trunk. Helson (1932), in studying residual sensation after operation for trigeminal neuralgia in Frazier's clinic, concluded that, *besides the deep sensation* of the facial nerve (nervus intermedius), certain fractions of temperature sense are transmitted over the sympathetic nerves. He and also Foerster, Altenburger, and Kroll (1929) claimed that this route plays an important part in residual pain after section of the Gasserian root and in atypical neuralgia. But attempts to relieve the atypical forms by resecting the superior cervical ganglion have been failures (Frazier, 1928; White and Sweet, 1952). Davis and Pollock (1932) have presented evidence that this ganglion carries nothing but efferent neurons and that its stimulation causes pain through a metabolic disturbance in the tissues, which, in turn, results in irritation of the ordinary sensory nerve endings. They found that they could relieve this pain in cats only through section of the posterior cervical and fifth cranial nerve roots. Recently White and Sweet (1952) have repeated this experiment in 7 patients in the course of superior cervical ganglionectomy under local anesthesia. Electrical stimulation of the ganglion with the chain intact produced definite pain in the face, head, or throat in 4. In 2, after the cervical trunk was divided just below the ganglion, the painful responses in the face persisted unchanged when the ganglion was stimulated; in a third pain was no longer present, although the pupil continued to dilate. In 3 in whom observations were made on stimulation of the caudal cut end of the chain, 1 felt nothing, the other 2 experienced pain in the lower neck or chest. From repeated disappointing experiences with diagnostic procaine block of the cervicothoracic ganglia and their resection in a number of cases, we have been convinced that the cervical sympathetic chain is not the usual route pursued by afferent impulses in atypical neuralgia. Where these impulses run and how to interrupt them still remains an unsolved problem. From the single observation reported above in which pain produced on stimulation of the superior cervical ganglion disappeared after the cervical trunk was sectioned, we cannot be certain that the cervical chain never serves as an accessory pathway in conduction of pain from the head, and we must mention a single case of bilateral unbearable neuralgia treated by White in collaboration with Dr. James B. Campbell in which repeated blocking of the cervical sympathetic fibers promptly stopped the pain on each occasion, and resection of the cervicothoracic ganglia on both sides has given a

surprisingly good result. This, we realize, is an exception to the rule, but it is reported for what it is worth.

Edith D., 41, MGH U-155885 BM, had undergone a series of operations for an atypical right-sided facial neuralgia by other surgeons. These included six injections of the infraorbital, maxillary, and mandibular nerves with alcohol; two resections of the retrogasserian root; and finally periarterial sympathectomy of the common and internal carotid arteries with ligation of the external branch. While stripping the periarterial plexus under local anesthesia, the surgeon had noticed that this reproduced her pain. None of these procedures gave more than a brief respite from her pain, which soon involved the opposite side as well.

She had then consulted Dr. Campbell, who found that left stellate ganglion block with procaine gave temporary complete relief. He repeated this on a number of occasions and then removed the left cervicothoracic and second thoracic ganglions through a supraclavicular approach. This was successful as far as her left-sided neuralgia was concerned, but right-sided pain developed and continued to increase until she was taking eight daily injections of Pantopon (60 mg) and had become seriously addicted.

After her admission to the hospital right-sided upper thoracic paravertebral block with procaine relieved her pain coincident with the appearance and duration of Horner's sign. Following removal of the first and second thoracic ganglia on 3/8/49, she was finally freed of pain. When last seen eighteen months later, she had been able to break her dependence on narcotic drugs and was leading a normal life without pain.

There is also a variety of cephalalgia which can be relieved by section of the external carotid artery or its temporal branch with their accompanying nerves Temporal arteritis is a form of vascular headache with tenderness over the artery, severe pain in the temple, conjunctival congestion, and excessive tear secretion. The pain may be throbbing, frequently unbearable, and is usually superimposed on a dull ache in the involved area. It characteristically occurs in periodic attacks The artery is tender to palpation, and relief can be obtained by compression of the carotid in the neck or by procaine infiltration of the periarterial plexus. In Nadler's (1945) account of 8 cases, 3 obtained sufficient relief by procaine block during the attacks, and 5 required resection of a segment of the artery. Haynes (1948) advocated additional interruption of the middle meningeal artery within the skull if the pain is deep-seated.

Pseudomotor Responses. Three interesting varieties of involuntary movements of the muscles of the face and tongue which may occur after injury of the oculomotor, facial, or hypoglossal nerves have been known for many years under the names of the physicians who first described them. These are the: (1) Marcus Gunn (1883) phenomenon, in which the

outer corner of the eyebrow is drawn up when the patient chews; (2) Heidenhain (1883) phenomenon, where the upper lip is retracted when the second division of the trigeminal nerve is stimulated; (3) Vulpian (1875) phenomenon of paroxysmal vasodilatation of the tongue, in which engorgement and slow movement of the paralyzed side of the tongue take place when the chorda tympani nerve is stimulated.

Lewy, Groff, and Grant (1937 and 1938) have investigated these phenomena in animals and have shown that the pseudomotor reactions which occur in the paretic eyelid, whiskers, or tongue can be reproduced by stimulating the mesencephalic root of the trigeminal nerve. When this group of cells is stimulated, an autonomic efferent discharge spreads over the peripheral distribution of the fifth nerve with the liberation of acetylcholine, which in turn produces a slow, tonic contraction of the paralyzed muscles. This is identical with the effect of injecting acetylcholine into the carotid artery under similar conditions (Bender, 1938). The responses of paretic striated muscle after degeneration of its nerve supply have been thoroughly investigated by Cannon and Rosenblueth (1949). These curious syndromes are probably produced in man by proprioceptive stimuli arising from movements of the face and jaw muscles with stimulation of the mesencephalic nucleus,* which sets off an autonomic discharge and liberates acetylcholine in the nerve endings of the face and tongue.

According to Wells (1946), about a hundred cases of the Marcus Gunn "jaw-winking" phenomenon have been reported. None has been seen by us at the Massachusetts General Hospital, but through the kindness of the U.S. Navy Medical Bulletin we are reproducing the typical example shown in Figure 50.

F. C. Grant (1936) has described a patient with congenital ptosis of his right eyelid in whom, from early infancy, curious associated movements had been observed whenever he chewed. During ordinary conversation they did not take place, but when the patient moved his jaws while eating the eyelid flew up, attracting the amused attention of those about him. Block of the third division and motor root of the right fifth nerve with procaine hydrochloride and subsequently with alcohol stopped the associated movements by preventing voluntary movement of the jaw muscles on the right and interrupting their proprioceptive fibers. Following intracranial section of the third division and the motor root, the "jaw-winking" phenomenon was relieved. From the Philadelphia investigations it would

* From a more recent investigation in which various areas of the pons and midbrain were stimulated, Corbin, Harrison, and Wigginton (1941) have concluded that the region which gives rise to this reflex parasympathetic discharge is not the mesencephalic root of the fifth but the reticular substance close to the intramedullary portion of the facial nerve.

appear that the reflex arc consisted of an afferent stimulus propagated over the proprioceptive fibers from the pterygoid muscles to the mesencephalic nucleus, and thence an efferent discharge over parasympathetic fibers with a resultant release of acetylcholine. The chemical action of this compound caused contraction of the partially paralyzed levator palpebrae muscle.




Fig. 50. The Marcus Gunn "jaw-winking" phenomenon.
Since childhood this patient had noticed wide retraction of the eyelids on the left whenever he opened his mouth. Slight ptosis, due to paresis of the left upper lid, can be seen in the photograph of the face at rest. (Reproduced from Wells, J. L. "The Marcus-Gunn syndrome: Report of a case" *U. S. Nav. med. Bull.*, Washington, 1946, **46**: 1275–1278.)

Ingraham and Campbell (1941), who performed a craniotomy in an epileptic child with this syndrome, were able to reproduce the phenomenon by cortical stimulation, but never without a preliminary contraction of the jaw muscles. On a somewhat similar principle of breaking an excessive vasodilator reflex in the side of the tongue in the presence of an ipsilateral partial paralysis of the face, Cobb and Mixter (1935) have recorded the successful surgical outcome in a patient with a Vulpian-like phenomenon, in whom the lingual nerve was first injected with procaine and later sectioned in the floor of the mouth.

This woman, who had had an incomplete section of the left trigeminal root performed seven years previously, had developed a postoperative facial paralysis. From this she had partially recovered, but she continued to complain of an atypical neuralgia which involved the left side of her head and neck.

As an additional unusual complication she was troubled by her tongue, which developed peculiar spasms on the anesthetic left side. These were brought on whenever she tried to chew or swallow dry food. Examination showed that the right half remained normal, while the left was turgid; it curled up and squirmed in slow, worm-like movements, which dragged the tongue backward into her left cheek. These attacks lasted several minutes, during which she was unable to speak, and were accompanied by a dull drawing pain in her tongue and throat. Since the lingual spasm was becoming so disagreeable, operation was advised with the knowledge that Vulpian's phenomenon in animals depended on stimulation of the chorda tympani fibers. Accordingly, on 11/16/29 Professor Leroy M. S. Miner of the Harvard Dental School resected a segment of the lingual nerve through the floor of the mouth under local anesthesia. Freedom from the pseudomotor attacks lasted for many years.



Fig. 51. The auriculotemporal syndrome.

Case reported in the text on p. 249, showing profuse sweating and vasodilatation which occurred on chewing. The phenomenon was seen on both sides and followed bilateral incisions at angles of jaw for drainage of parotitis in infancy.

This human observation differs in only one respect from the pseudomotor phenomena which have been produced experimentally in animals—the striated musculature of the tongue had not been sensitized to acetylcholine by degeneration of the hypoglossal nerve. Here the mechanism must have depended on sensitization of the smooth muscle of the lingual blood vessels, which receives vasodilator fibers over the seventh, chorda tympani, and lingual nerves.

Two other peculiar autonomic disturbances are seen occasionally after injuries of the nerves in the face:

1. The so-called "auriculotemporal" syndrome follows inflammation or trauma to the parotid gland with injury to the regional nerves. During eating there is pain in the gland, with vasodilatation and sweating in the region of the temple and cheek. This reaction has been explained by List



Fig. 52. Restoration of effective closure of eyelids in peripheral facial palsy following superior cervical ganglionectomy.

Mrs. Grace B., MGH U-669804 BM, had suffered for fifteen years from intermittent spasm of the right facial muscles. Owing to a congenital defect in the left eye, she was unable to see when her eyelids contracted. To relieve frequently recurring episodes of blindness and her unsightly grimaces, the right facial nerve was divided and a faciohypoglossal suture was performed on 7/19/49. At the same time the superior cervical sympathetic ganglion was resected. These photographs, taken two weeks after the operation, show that voluntary closure of the lids on the right was nearly complete despite the complete peripheral paralysis of the facial nerve.

and Peet (1938*D*) on the basis of hypersensitivity of the cholinergic salivary and sudomotor fibers, which react to the chemical mediator substance liberated in the course of mastication. This response fits in with the theory proposed by Lewy and his colleagues (1937 and 1938) quoted above. The response is always elicited by chewing movements. According to their concept, the syndrome of parotid discomfort and facial sweating is caused by a reflex activated by proprioceptive fibers in the masticatory muscles (and possibly in taste fibers as well) with its effector arc carried from the mesencephalic nucleus of the trigeminal to sympathetic axons in

the auriculotemporal nerve. The acetylcholine released around denervated sensitized secretory cells in the parotid and affected sweat glands is a satisfactory explanation of the observed phenomenon. Freedberg *et al.* (1948), who studied the syndrome in two patients after parotitis with incision and drainage, found sweating of the involved side following the injection of significantly higher dilutions of acetylcholine, and they stated that the reaction was abolished after blocking the auriculotemporal nerve with procaine. They also concluded that the syndrome is probably related to denervation sensitivity of the sweat glands. The following case history illustrates this unusual syndrome:

Alex P., 9, was seen by one of us in consultation because he sweated so excessively "in front of his ears" and over the region of both parotid glands. This occurred whenever he made chewing movements and was accompanied by a striking vasodilatation of the involved area of skin. The response did not appear to be evoked by any specific gustatory stimulus, as it was elicited as well by chewing paraffin as more tasty food. He was brought in by his father not for treatment, as the phenomenon caused him no discomfort, but because of the interest of Dr. Bronson Crothers of the Children's Hospital, who was treating him for another condition. When he was twelve days old he had developed a "stomatitis with abscess formation in both cheeks," which had been drained through small incisions over the lower border of each parotid. The father did not have time to permit any studies with nerve block or determination of sensitivity to acetylcholine, but we were able to obtain excellent photographs of this unusual condition (Fig. 51).

A somewhat similar situation was observed in a young housewife who had had a parotid tumor excised. Perspiration was so profuse in the region of the scar that for several weeks she was thought to have a salivary fistula until this syndrome was recognized.

Another sudomotor response of considerable academic interest is the phenomenon of "gustatory sweating." In rare instances, after upper thoracic sympathectomy, the patient may notice a tendency for sweat to break out over the face and scalp. It has been well described by Haxton (1948) from Professor Telford's clinic in Manchester. The syndrome may develop spontaneously, Claude Bernard being a classical example. Flushing and sweating are produced on eating highly spiced foods or chocolate. After sympathectomy the appearance of the phenomenon is indicative of incomplete denervation * or regeneration, as it can be interrupted by procaine block of the cervical sympathetic trunk. This response is closely

* According to the orthodox view the preganglionic sudomotor outflow to the head arises from the upper two thoracic spinal roots Goetz (1948*B*), however, has shown that in 40 per cent of persons there may be a supplementary origin from C8 or T3 and T4.

1. The so-called "auriculotemporal" syndrome follows inflammation or trauma to the parotid gland with injury to the regional nerves. During eating there is pain in the gland, with vasodilatation and sweating in the region of the temple and cheek. This reaction has been explained by List



Fig. 52. Restoration of effective closure of eyelids in peripheral facial palsy following superior cervical ganglionectomy.

Mrs. Grace B., MGH U-669804 BM, had suffered for fifteen years from intermittent spasm of the right facial muscles. Owing to a congenital defect in the left eye, she was unable to see when her eyelids contracted. To relieve frequently recurring *episodes of blindness and her unsightly grimaces, the right facial nerve* was divided and a faciohypoglossal suture was performed on 7/19/49 At the same time the superior cervical sympathetic ganglion was resected. These photographs, taken two weeks after the operation, show that voluntary closure of the lids on the right was nearly complete despite the complete peripheral paralysis of the facial nerve.

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stimulation flattens the lens and accommodates the eye to distant objects, whereas the parasympathetic aids in focusing on objects at close range. The effect of sympathetic paralysis is not usually sufficient to make the subject obviously myopic, but is apparent on optometric examination.

A fifth rare component of the Claude Bernard–Horner syndrome is the lack of pigment deposition in the iris. Evidence is accumulating from both laboratory and clinical observations (Simeone, unpublished data) that the sympathetic paralysis of the eye must occur at birth or must be antenatal in order for the lack of pigmentation to become apparent.

Horner's sign is seen clinically after any form of cervical sympathectomy, but it is incomplete when only the first thoracic ganglion is resected. Injury to the sympathetic chain below this level causes no oculopupillary change. DeJong (1935), who has written a valuable article on the occurrence of the condition in the clinic, gives the following etiological factors in order of frequency: The most common causes are tumors of the spinal cord, or syringomyelia at the level of the ciliospinal center. Next in order are cervical rib, cervical tumor or enlarged lymph nodes, aortic aneurysm, tumors of the upper mediastinum, disease of the pulmonary apices and, more rarely, radiculitis, disease of the esophagus, and adenoma of the thyroid gland. The condition frequently follows trauma, especially in the form of bullet or stab wounds (Cobb and Scarlett, 1920) and the lower brachial plexus form of birth injury (Klumpke type). A hereditary form of Horner's syndrome associated with unilateral facial atrophy and involvement of the brachial plexus has been described by Wechsler (1927). Lesions causing the syndrome through injury of the descending pathway in the brain stem, medulla, and upper cervical cord have been recorded by Wechsler (1927), Riley (1940), Grinker (1937), Winther (1932), Foerster (1936), and Duthie and Mackay (1940).

The ptosis which accompanies Horner's syndrome paralyzes the tonic innervation of the smooth muscle in the upper eyelid. Sicard and Robineau (see Rosenblueth, 1927) first suggested resection of the superior cervical ganglion as a palliative procedure for patients with severe facial palsies. After this operation the upper eyelid can be brought down to cover the cornea by relaxing the levator palpebrae muscle, which is under control of the oculomotor nerve. This has been put to very practical use by Leriche (1926), Hesse (1930), and ourselves. A photograph illustrating the extent to which the upper eyelid can be closed to protect the sclera and exclude light is reproduced in Figure 52.

Exophthalmos. Human exophthalmos is due to retrobulbar pressure. In exophthalmic goiter, however, it was formerly believed that the protrusion

related to the auriculotemporal syndrome, and the reflex is presumably mediated through regenerating cholingeric sympathetic fibers, the acetylcholine liberated at their terminations producing an excessive response in adjacent sensitized glands.

2. The phenomenon of "crocodile tears," in which there is excessive tear secretion on eating after partial injuries to the central portion of the facial nerve, may likewise be accounted for on the basis of injury to the lachrimal fibers, which enter its great superficial petrosal ramus, with resultant sensitization of the tear gland to the diffuse liberation of acetylcholine which occurs, according to Lewy, Groff, and Grant (1937, 1938), during mastication. This phenomenon has also been ascribed by Ford and Woodhall (1938) and Russin (1939) to aberrant regenerating fibers of the facial nerve, so that some of the autonomic fibers which once entered the chorda tympani in their course to the salivary glands become misdirected and follow the lachrimal fibers over the great superficial petrosal and vidian nerves (see p. 40). Russin states that the tearing does not occur with pure masticatory movements but requires the added stimulus of bitter, sour, or salty foods. It is quite possible, however, that taste as well as proprioceptive stimuli may give rise to a parasympathetic discharge.

Horner's Sign. This syndrome, which should more correctly be referred to as the sign of Claude Bernard–Horner, denotes a paralysis of the sympathetic fibers to the eyelids and iris. The condition, which was described in animals by Claude Bernard (1852) and in man by Horner * (1869), is commonly supposed to consist of pupillary constriction, ptosis, and enophthalmos. Recent work necessitates some modification of these three cardinal signs and the addition of two others of lesser importance. Mutch (1936), by taking flashlight photographs of patients with cervical sympathetic paralysis, has shown that pupillary constriction gives way to moderate dilatation in total darkness. The narrowing of the palpebral fissure results both from drooping of the upper lid and raising of the lower. Enophthalmos, while definite in lower animals, is apparent rather than real in man. This question was settled by placing an exophthalmometer in position during an operation and stimulating the cut peripheral end of the sympathetic trunk. Though dilatation of the pupil occurred at once, no forward movement of the eyeball could be detected. This point has been corroborated by Pochin (1939).

A fourth feature has been described by Byrne (1934) and Cogan (1937) and concerns visual accommodation. Cogan points out that sympathetic

* It is of historical significance that, a generation before Horner, Hare (1839) gave an accurate clinical description of this sign in a case of tumor compressing the cervical sympathetic trunk.

of vasoconstriction in the cerebral vessels and, conversely, resection of the upper cervical chain a moderate vasodilatation. This, however, is far less than in the peripheral arteries. These investigators have also observed in their direct measurements through brain-window preparations that vasodilatation after sympathetic paralysis is much less than when the animal is given small amounts of carbon dioxide to inhale.

Leriche and Fontaine (1936) first proposed blocking the cervical sympathetic trunk for the treatment of vasospasm after acute cerebral vascular accidents. De Takats (1949*B*) claims that there is no doubt from his clinical experience that recovery in patients who have very recently suffered an apoplectic stroke from either cerebral thrombosis or embolism can be accelerated by procaine block of the cervical sympathetic trunk. The injection must be performed on the side of the infarct at the earliest possible moment and should be repeated at daily intervals if there is evidence of improvement. He reports 105 injections in 50 patients and states that consciousness was regained in 6, speech improved in 17, and motor power increased in 8. Amyes and Perry (1950), who have also blocked the stellate ganglion in 50 cases of acute cerebral thrombosis and embolism, report improvement in 28 of 44, and in 9 out of 10 where the treatment was started within the first six hours. In those who improved there was a change in motor power and speech, if the dominant hemisphere was involved.

An extensive report on this method of treating cerebral thrombosis and embolism was given by Naffziger and Adams (1950) at the 1949 meeting of the Western Surgical Association, and further impressive results were contributed by the discussers of the paper. Although they found that stellate block failed to exert a consistent influence on cerebral blood flow and cerebrovascular resistance, as measured by the nitrous oxide technique of Kety and Schmidt (1948), their clinical reports in 155 cases indicate an immediate good response in 59 per cent after the appearance of a Horner's sign. An additional 24 per cent showed some worth-while improvement, and only 17 per cent failed to benefit. They also report favorable results in traumatic and postoperative cases suffering from impaired circulation of a hemisphere. No untoward effects were encountered in over 700 injections. Many patients received a number of successive blocks, while in the latter part of the series a small catheter was inserted through the needle and left in place for repeated instillation of procaine. In cases benefited clinically, there was usually a corresponding improvement in the electroencephalogram, as well as increase in the strength of the grip recorded by dynamometer measurements. These authors did not

of the orbit was due at least in part to the effect of sympathetic stimulation. For this reason many cervical sympathectomies were performed in the belief that the eyeball would recede (Jonnesco, 1923). This procedure proved unsatisfactory. From the evidence reported in the preceding section, it is now realized that the smooth muscle which protrudes the eyeball in animals is rudimentary in man. In addition, Naffziger (1938) and Brain (1938) have shown that in thyrotoxicosis the exophthalmos is due to swelling of the retrobulbar cone and can be relieved only by orbital decompression or by reducing the excessive secretion of pituitary thyrotropic hormone.

Retinitis Pigmentosa. Dilatation of the retinal arteries after cervicothoracic ganglionectomy has been reported by Wagener (1931). Royle (1930 and 1932*B*) has utilized this effect in an attempt to improve the blood supply to the retina in cases of pigmentary degeneration. Here the arteries appear as mere threads, and the patient suffers from night blindness and extreme contraction of his peripheral fields of vision. Royle reports that this operation in 6 cases has produced a moderate improvement in visual acuity, as well as an enlargement of the visual fields. The relief was more marked in younger patients and in early forms of the disease.

In our hands 3 patients submitted for operation by the Massachusetts Eye and Ear Infirmary derived no demonstrable improvement. These were all young women at a moderately advanced state of the disease. Further studies on earlier cases have shown no demonstrable dilatation of the retinal vessels after paralysis of the ocular sympathetic fibers with procaine. Verhoeff (1931) has had the opportunity to make a microscopic examination of the eye in this disease. In his description of the pathological changes he states that as the retinal vessels run outward from the optic disk their adventitia increases in thickness. Anterior to the equator of the eye the vessels are converted to solid strands of hyaline connective tissue. With a knowledge of these organic changes in the blood vessels, sympathectomy seems definitely contraindicated for this condition. The lack of favorable reports in current medical journals is evidence that this view is shared by the majority of the profession.

Sympathectomy in the Treatment of Cerebral Thrombosis and Embolism. Surrounding an ischemic area after cerebral embolism or thrombosis, there is a zone of stasis with contraction of the pial vessels around the infarct This has been observed through a brain window in animals by Villaret and Cachera (1939).

The experimental studies of Cobb and others (summarized by Cobb, 1933) have shown that sympathetic stimulation can produce a mild degree

ment should not be attributed to sympathetic block. When improvement appears immediately after the appearance of Horner's sign, a fine polyethylene catheter can be inserted through the needle and left *in situ* for repeated injections of 1 per cent procaine at two-hour intervals (see p. 478). We are still not convinced that inhalation of low concentrations of carbon dioxide (5 per cent in oxygen) is not a more effective cerebral vasodilator, and we are planning a thorough investigation.

Sympathectomy in the Treatment of Spastic Paralysis. The treatment of spastic paralysis by sympathectomy, proposed by J. I. Hunter (1924) and Royle (1924*A* and *B*), has failed to stand the test of time. A complete review of the arguments which have proved that this operation has no physiological basis was given in the second edition of this monograph. As it is now generally agreed that no reduction in the spastic state can be achieved by this operation and no further interest in the subject has been taken in recent years, we have decided not to include these data in this edition.

resort to sympathetic block until intracerebral bleeding had been ruled out by lumbar puncture, and they observed remarkable improvement even at long intervals after the cerebral vascular accident. In 15 cases improvement in late hemiplegia, even after intervals of several years, has led them to perform a cervical sympathectomy.

To date the Anesthesia Service of the Massachusetts General Hospital has treated 12 cases after cerebral vascular accidents. In 8 of these with typical history and signs of cerebral thrombosis or embolism, sympathetic procaine block was performed within a few hours of the onset of symptoms and in the others after longer intervals. Two or more injections were usually made. None showed any improvement of hemiplegia or aphasia that could be ascribed to the injection, although all developed a prompt and satisfactory Horner's sign. The only promising result in the series was in a young woman who was developing hypesthesia and weakness of the left arm seventeen days after carotid ligation for a cerebral aneurysm. In this case the signs of cerebral ischemia promptly cleared and did not recur, so that it was impossible to repeat the injection with inert saline solution. This woman was a nurse who was aware of and feared this possible complication of carotid ligation, so that without a control injection it is manifestly impossible to rule out the effects of suggestion. We have also treated cases of sudden hemiplegia which developed at the time of Diodrast arteriography with procaine block of the cervical sympathetic trunk. Cerebral ischemia following injection of radiopaque iodine compounds is a rare but well-known complication, which appears to be caused by vascular spasm.* Accidents of this sort should therefore respond to this treatment, provided interruption of sympathetic constrictor impulses is capable of relaxing spasm of this kind. In 4 cases so treated to date under the care of Dr. W. H. Sweet on the Neurosurgical Service of the Massachusetts General Hospital (unpublished data), there has been no visible improvement in the few hours following the repeated procaine blocks, although all 4 of the patients improved slowly during a period of weeks. Our experience to date has left us unconvinced of the value of this procedure.

After reading Naffziger and Adams' (1950) careful report we are nevertheless ready to concede that the method deserves thorough and careful trial. In view, however, of the known vagaries of cerebral vascular accidents and the tendency to spontaneous recovery, gradual late improve-

* A recent patient at this hospital became temporarily blind after Diodrast arteriography. Ophthalmoscopic examination by Drs J. J. Michelsen and D. G Cogan revealed intense spasm of the retinal vessels. This fortunately cleared within a few hours synchronously with return of normal vision.

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CHAPTER XI

Heart and Aorta

I. Innervation

The first important experiment on cardiac sensation was recorded by Goltz (1863). The experimenter was William Harvey, and the subject the young son of Count Montgomery, a friend of King Charles I, who had received a severe wound in the chest as a child. Although the thoracic cavity had been opened widely, the accident had not ended in death but in healing, with the heart exposed in an open hole. On taking off a sort of protective cuirass, Harvey saw the exposed beating heart. Touching the heart caused not the slightest sensation. A similar modern observation has been put on record by J. Alexander, Macleod, and Barker (1929), who studied a patient with open drainage of the pericardium which exposed the lower portions of the ventricles and the diaphragm. They also found the ventricles to be insensitive to touch. Rubbing felt like pressure, and heavy pressure and pricking like touch. Heat, cold, and vibrations were not perceived at all, and electrical stimulation evoked sensation only when it produced extrasystoles. Stretching, pricking, or scratching the parietal pericardium, however, caused severe pain.

These observations are in line with Lennander's (1901) findings that the viscera are insensitive to cutting, crushing, and even burning, but that the parietal peritoneum has acute sensation. It is now recognized that the physiological stimulus of cardiac pain is anoxemia and the products of fatigue (Sutton and Lueth, 1930; R. M. Moore and Greenberg, 1937; Blumgart, Schlesinger, and Davis, 1940).

It has been pointed out in Chapter VI that, although the true autonomic fibers carry only motor impulses, all the nerves to the internal organs are mixed nerves and contain a certain number of somatic sensory in addition to a far greater proportion of autonomic motor axons. Leriche (1925*B*), while operating under local anesthesia, was able to show that electrical stimulation of the upper pole of the stellate ganglion caused radiation of intense pain to the arm, whereas when the lower half of the ganglion was stimulated the patient felt pain over the precordium in the second and third intercostal spaces.

In the classical anatomical texts, from Neubauer's (1772) beautiful plates (Fig. 3) down to the late 1920's, only the cervical cardiac nerves are shown. Three distinct trunks, the superior, middle, and inferior cardiac nerves, are given off from the corresponding sympathetic ganglia and descend to form the deep cardiac plexus. A variable number of small branches join the plexus from the vagi. In certain animals the vagus gives off a distinct depressor branch, but in man this structure is rarely found as a separate entity. Langley (1892), in an investigation of the segmental origin of the thoracolumbar sympathetic nerves, showed that accelerator impulses leave the cord by the upper five pairs of anterior roots and their white rami. He assumed that all efferent impulses then traveled upward in the sympathetic chain to form synapses in the three cervical ganglia and send their postganglionic axons to the heart through the cervical cardiac nerves.

Cannon, Lewis, and Britton (1926), in attempting to prepare a totally denervated heart, noticed that accelerator stimuli of nervous origin reached the heart even after resection of both cervical sympathetic chains down through the stellate ganglia. Later, White, Garrey, and Atkins (1933) obtained as much as a 58 per cent acceleration in the heart rate on faradic stimulation of the second and third thoracic ganglia after division of the trunk above this level.* The explanation of these findings lies in the existence of the thoracic cardiac nerves which form direct connections between the upper four or five thoracic ganglia and the heart. This important anatomical discovery, which accounts for the failure of many operations in angina pectoris, was made almost coincidentally by Braeucker (1927) (Fig. 14) and by Jonnesco and Enarchesco (1927), and was later corroborated by Kuntz and Morehouse (1930).† Saccomanno (1943) found that the thoracic cardiac nerves contain twice as many fibers to the cardiac plexus as the contribution from the cervical sympathetic.

The vasomotor nerves of the coronary arteries, in order to maintain homeostasis, probably function in an opposite manner from those to the cutaneous and splanchnic vessels. Working with dogs, Anrep and Segall (1926) demonstrated by measuring the outflow of the coronary sinus that stimulation applied to the vagi causes constriction of the coronary arteries, and applied to the sympathetic causes dilatation. These findings were confirmed by Gollwitzer-Meier and Krüger (1935), who measured blood flow

* In these experiments all other sources of cardiac stimulation were eliminated by section or atropinization of the vagi, resection of the adrenal glands, and transection of the spinal cord at the third cervical segment.

† In a recent historical review of the discovery of the thoracic cardiac nerves, G. A. G. Mitchell (1949) finds that Weber first depicted small cardiac rami arising from the second, third, and fourth thoracic ganglia in the calf in 1815, and that Swan first described them in man as long ago as 1830!

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sion unanesthetized dogs showed obvious signs of discomfort * and characteristic respiratory changes within fifteen to thirty seconds; the latter were recorded graphically on a smoked drum. The effects of various neurosurgical procedures on the pain of coronary ischemia were tested in a series of 21 animals. It was shown that cutting the vagi or the upper six pairs of intercostal nerves had no effect on the pain produced by transitory ischemia of the myocardium. Bilateral stellate ganglionectomy resulted in only a slight reduction of the sensory stimulus. On the other hand, dogs showed no sign of discomfort after resection of the four upper thoracic sympathetic ganglia or the upper five pairs of posterior spinal roots. These experiments, together with the recent anatomical discovery of the thoracic cardiac nerves, explain why cervical sympathectomies have failed so often to relieve angina pectoris.

The nerve supply of the aorta and other large arteries of the trunk is derived from the paravertebral ganglia in a segmental manner. In contradistinction to the peripheral vascular innervation, the visceral nerves are closely grouped around the blood vessels.

II. Neurosurgical Treatment of Angina Pectoris

Surgeons are indebted to François-Franck (1899), professor of physiology in Paris, for the suggestion that removal of the cervical sympathetic chain would give relief from cardiac pain, † and to Jonnesco (1920) in Bucharest for the pioneer attempts to carry this out in severe angina pectoris. His first and one of the most successful cases was operated upon in 1916. Because early attempts by the Rumanian surgeon and others were not consistently successful, Sir James Mackenzie (1925) stated that discussions on the painful mechanism involved in angina pectoris were usually futile, as they simply consisted of the replacement of one speculative hypothesis by another. Up to the time of his death in 1925 this criticism was perfectly just. To understand the state of confusion at this period one need only recall the number of operations which had been advocated on the cervical nerves and the divergent theories which had been proposed by their authors. The fact that all these methods were reported to have given good results in

* For want of a better word to describe the characteristic reaction to coronary occlusion of this duration, the phenomena described above will be referred to hereafter as signs of cardiac pain. But it is most important to emphasize that none of these animals was ever permitted to suffer acutely, although it was evident in each that this would have occurred if the stimulation had been prolonged.

† François-Franck appears to have been the first physiologist to recognize the role of the cervicothoracic sympathetic rami as the afferent pathway of cardio-aortic pain. He investigated the sensitivity of the aorta in experimental animals and concluded that "cette notion nouvelle de la sensibilité aortique transmise par le sympathique thoracocervical suggérera peut-être l'idée de pratiquer la résection dans l'angine de poitrine."

in the coronary arteries by the thermostromuhr of Rein. Greene and Atkins (1931) have found that in dogs adrenaline dilates the coronary arteries. On the other hand, Kountz, Pearson, and Koenig (1934) have made a series of extremely interesting perfusion experiments on the revived human heart and have been able to duplicate Anrep and Segall's findings in dogs only when there was dissociation of auricular and ventricular contraction, so that the rate was not influenced by the nerves. In the normally beating human heart vagus stimulation slowed the rate and increased the coronary flow, while sympathetic stimulation accelerated the heart rate and reduced the flow. Further observations on the innervation of the coronary arteries have been reported by Katz and Jochim (1939). From their measurements of changes in coronary flow in a preparation consisting of the fibrillating heart of a dog, they concluded that:. (1) The vagi carry only cholinergic coronary vasodilator fibers. (2) The stellate ganglia send to the heart adrenergic coronary dilator and constrictor fibers, both of which are tonically active; but in their opinion the tonic action of these nerves is predominantly vasoconstrictor.

We must therefore admit that no final conclusion has been reached on this problem because of the difficulties in controlling all the variables involved, as Gregg (1946) has pointed out in his review of the factors influencing the coronary circulation. It is our personal opinion that the most valid experiments are those of Anrep and Segall and of Gollwitzer-Meier and Krüger cited above. Their determinations were made on relatively normal hearts, whereas findings on such abnormal preparations as the revived human heart and the fibrillating dog's heart must be regarded with a certain degree of suspicion.

The sensory axons from the heart appear to follow essentially the same paths as the efferent supply. The same general principles apply to the perception of cardiac pain as to other types of visceral sensation (see Chap. VI). Cardiac pain is characteristically felt in the precordium and referred to one or both arms, less frequently to the neck and jaws. This is often associated with tender spots over the chest wall. Heinbecker (1932) has shown that all the cardiac nerves (with the exception of the superior) contain myelinated fibers of intermediate size and with electrical properties identical with those of nerves which carry somatic sensory impulses.

White, Garrey, and Atkins (1933) investigated the pathways of cardiac pain in dogs. By the use of a preparation suggested by Sutton and Lueth (1930) it was possible to shut off temporarily the flow of blood in the descending branch of the left coronary artery. After acute coronary occlu-

Another possible method of reducing anginal attacks is by interrupting motor impulses which drive the heart to exceed its limited capacity for work in the presence of an inadequate coronary circulation. This will actually be accomplished along with sensory denervation if the sympathetic ganglia are removed down through the fifth thoracic. This is discussed below (p. 294) in connection with complicating anginal attacks in hypertension. Smithwick has found that heartbeat is slowed just as effectively by bilateral ganglionectomy from T2 to T5 as after more extensive sympathectomy which includes the nerve supply to the adrenals as well. While this operation results in a slower heart rate at rest, necessary acceleration on exertion is still possible through vagal inhibition. The work of the heart can also be reduced by lowering thyroid activity. To this end the desired degree of myxedema can be induced with greater accuracy and safety by thiouracil than by total thyroidectomy, formerly advocated by Blumgart, Levine, and Berlin (1933).

We have, however, always maintained that the logical point for neurosurgical intervention is the sensory pathway. The problem of what and how much to cut was at first hopelessly confused by the inconsistent results of cervical sympathectomy. The only possible conclusion to be drawn from the older statistics is that the nerve connections to the heart were only partially interrupted. Mandl (1925*B*) and Swetlow's (1926*B*) method of paravertebral injection of the thoracic sympathetic ganglia and the physiological demonstration by White, Garrey, and Atkins (1933) of the thoracic cardiac nerves pointed out the solution of this difficulty.

The experimental observations described above and the excellent clinical results which have followed destruction of the upper thoracic ganglia or the posterior spinal roots have completed the chain of evidence and prove that cardiac pain can usually be relieved by properly devised neurosurgical operations. Our present knowledge of the pathways of cardiac pain is illustrated in Figure 53. This diagram shows that sensory impulses traveling in the cervical sympathetic nerves do not enter the cord until they descend to the level of the highest white rami in the thoracic region.* With this

* Heinbecker (1933) has claimed that he has been able to detect direct sensory connection between the cervical sympathetic ganglia and the spinal cord. Our experience with cardio-aortic pain referred to the cervical plexus and head has convinced us that this cannot be interrupted by resection of the cervical sympathetic trunk (see Case 5A, below). Saccomanno *et al* (1947), from experiments in which they stimulated the anterior spinal roots in dogs, claimed that no demonstrable accelerator fibers leave the cord over the first thoracic root. In our opinion the results of animal experiments of this sort cannot be applied to man. Their added assumption that the segmental distribution of sensory afferent fibers must correspond with the motor outflow seems totally unwarranted. Until proved otherwise in man, surgeons should continue to resect the first thoracic posterior root or its corresponding ganglion through which the upper cardiac afferent axons pass.

some cases and to have failed completely in others added even further difficulties. The reader who wishes to familiarize himself with these different procedures is referred to the writings of Jonnesco (1920), Leriche and Fontaine (1932*A*), Danielopolu (1927), Coffey and Brown (1923), Richardson and P. D. White (1929), and many others. Reid and Andrus (1925) reviewed the various forms of cervical sympathectomy, and Fontaine (1925) and Cutler (1927) made statistical studies of results culled from the general literature. Their independent figures showed that only some 60 per cent gained adequate relief.

In an attempt to explain the inconsistent results of these operations, recent anatomical findings should be re-emphasized. It is probable that the Jonnesco procedure of complete cervical sympathectomy and also Leriche's method of stellate ganglionectomy result in an interruption of the major portion of the afferent pathways from the heart in a large percentage of cases. This has been emphasized in an excellent article by Govaerts (1936). But the cervical operation is bound to fail when the accessory pathway through the thoracic cardiac nerves is well developed. Why resection of the superior cervical ganglion alone, as recommended by Coffey and Brown (1923), should have relieved a certain number of cases of angina pectoris remains a mystery. No afferent axons have been found in the upper portion of the cervical sympathetic trunk (see Chap. III). The only plausible explanation which has been put forward is that the greater portion of the coronary constrictor fibers runs through the superior cardiac nerve, and that its interruption increases the irrigation of the myocardium. In view of recent physiological findings, however, it is questionable whether this explanation can be correct.

In evaluating neurosurgical procedures for the control of angina pectoris in the light of present anatomical and physiological concepts which have been outlined above, three possible points of attack must be considered.

1. Vasomotor nerves: Prevention of vasoconstrictor spasm in the coronary arteries
2. Motor accelerator nerves: Interruption of cardiopressor reflexes
3. Sensory nerves. Interruption of pain pathways

The first of these methods must be regarded as of dubious value, because at the present time physiological evidence concerning the action of the cardiac nerves on the coronary circulation is too conflicting to permit any neurosurgical attempt to increase the blood supply of the heart muscle (Gregg, 1946). Furthermore, even if it were feasible it would not often be a practical procedure, as in the great majority of patients with angina pectoris the resilience of these arteries has been lost.

in mind it is clear that the upper three or four thoracic ganglia, their communicant rami, and the posterior spinal roots are the focal points through which all cardiac pain must pass. Destruction of any of these structures will interrupt the afferent pathways from the left or right side of the heart.

After a complete unilateral sympathetic denervation of the heart, cardiac pain may continue to radiate to the opposite arm or precordial region, but it stops at the mid-line. Wyburn-Mason (1950) claims that the heart, embryonically a mid-line structure, has nervous connections with the two sides of the body which correspond to its right and left components. The left auricle and ventricle, pulmonary veins, interatrial septum, and atrioventricular node receive a left-sided innervation; while the chambers on the right and sinoatrial node derive their supply of nerves from this side. In the typical case of anginal pain of coronary insufficiency, the vascular changes and infarction involve the left side of the heart, which is usually much more affected than the right. In these circumstances the pain is referred largely or entirely to the left side; a left-sided denervation will give effective relief if the right ventricle is not too seriously involved. This author cites a case of dextrocardia with coronary disease in which pain was entirely right-sided, but we have completely relieved several cases of purely right-sided angina pectoris with the heart in the normal position by denervation limited to that side. We have evidence also that the innervation of the ascending arch of the aorta comes from the right side and that of the transverse and descending arch from the left (see p. 287).

During the past twenty-two years we have treated 94 patients with intractable cardiac pain along the lines just described at the Massachusetts General Hospital and 65 patients with angina pectoris in conjunction with primary hypertension at the Massachusetts Memorial Hospitals. Patients have been transferred by the cardiac consultants after a thorough trial of medical treatment has failed to bring adequate relief of severe angina pectoris. The only requisite has been really severe and frequent bouts of pain. Few have been refused surgical treatment because of recent coronary infarction or threatened cardiac failure. Milder cases which could be maintained in even relative comfort on a medical regime have not been accepted. Few were able to perform any kind of work, and 22 were having many attacks while at rest in bed; 31 presented clear evidence of previous coronary occlusion, and a number were in active congestive failure.

In the treatment of these cases surgical excision of the upper thoracic ganglia is capable of giving most satisfactory relief of characteristic pain in the precordium and arm on the side of operation. Prior to 1939 we used the posterior approach described by White, Smithwick, Allen, and Mixter

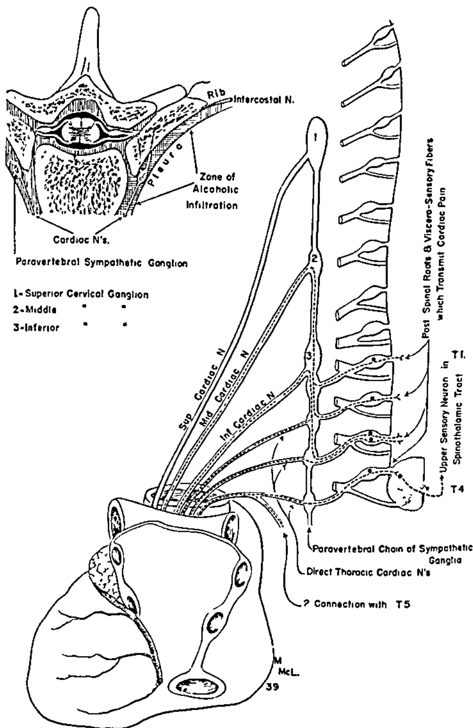


Fig. 53. The sensory nerves of the heart.

In this diagrammatic representation afferent fibers from the vagus are not shown, because they play no role in cardiac pain. There are possibly afferent fibers in the superior cardiac nerve, but if present they must establish connections with the cranial and upper cervical nerves rather than descend in the cervical sympathetic trunk (see Davis and Pollock, 1932). Although a thoracic cardiac ramus is shown arising from the fourth thoracic ganglion, it is questionable how often it exists (Reproduced from White, 1940, by permission of *Surg., Gynec. & Obst.*, Chicago)

postoperative reaction, must be done on the conscious patient, who is thereby submitted to psychic disturbances which can readily bring about fatal infarction in the most advanced degrees of coronary disease. Nevertheless, we still prefer to block the poorest-risk cases with angina decubitus, syphilis of the aortic arch, or cardiac decompensation, or the very elderly individual who cannot be kept in bed.

Thoracic Ganglionectomy. Results of sympathetic ganglionectomy in our 14 cases are summarized in Table XIV. All had effective immediate relief of pain. Operative mortality, counting deaths in the hospital, has been 14.3 per cent, a greater incidence than the 6.8 per cent hospital mortality cited by Lindgren and Olivecrona (1947). Only a single death, however, has occurred in the last 9 operations since the routine use of intratracheal ether in the lateral oblique position. This rate of mortality corresponds almost exactly with that reported by Morrison (1948) for general surgical procedures in patients with coronary disease. The histories of 3 patients are given below. The first illustrates the completeness of the left-sided denervation by the fact that in the eventual fatal coronary thrombosis intense pain involved the right arm and precordium but never crossed the mid-line. Mackenzie might have claimed that this young man's life was shortened by surgical relief of his pain, but death was caused by his own neglect and not by any lack of adequate warning that he was overtaxing his heart.

Case IA. Giuseppe G., 20, MGH #270156. Rheumatic heart disease, mitral stenosis, and regurgitation; also aortic stenosis and regurgitation with angina pectoris.

This young man first entered the hospital with rheumatic fever in 1925. At that time he already had signs of cardiac involvement with aortic regurgitation. In 1928 he experienced precordial pain on drinking cold water. Since then the attacks had remained localized to the left precordium, but increased in number and severity. The attacks were particularly troublesome at night (four to six attacks) and lasted as long as an hour.

Examination revealed a pale, thin young man with arterial pulsations in his neck, a thrill over the great vessels, and a systolic and diastolic aortic murmur. There was no evidence of cardiac failure. The heart was moderately enlarged. Electrocardiogram showed a diphasic T_2 and left axis deviation.

1/28/29 Diagnostic procaine block of first and second thoracic ganglia, followed by relief for twenty-four hours.

2/5/29: Resection of central end of second rib with first and second thoracic sympathetic ganglia on left side. Drs. W. J. Mixter and J. C. White.

The patient made a smooth convalescence. His left-sided anginal attacks were permanently relieved, but he continued to have mild bouts of pain in his right chest which served as an adequate warning signal. He left the hospital and continued to work as an insurance agent, paying no attention to

(1933) to resect the central portion of the second rib and the upper three thoracic ganglia. This operation, then performed in the prone position, was found to be too dangerous in patients with advanced coronary disease. Respiratory exchange is greatly reduced with the weight of the patient on his chest and abdomen; as a result, the return of venous blood to the heart is impaired, and dangerous falls in blood pressure are a common occurrence. This is not the case when operation is performed with the patient on his back or side.

For the above reason, at the time of writing the second edition we advocated the supraclavicular approach, as first described by Gask (1933), in which the patient is placed on his back as in a thyroidectomy. With this exposure, in which the anterior scalene muscle is divided, the apical pleura can be freed to a point below the third rib and the sympathetic trunk resected from the middle cervical through the third thoracic ganglion or further. This approach has been employed by Lindgren and Olivecrona (1947), but we have not found it so convenient for exposure of the third and fourth thoracic ganglia, which should both be resected. Failure to carry this out resulted in the continuation of low precordial pain in Case 6A (see below) and in some other late recurrences. We have recently found that the upper thoracic ganglia can be exposed most satisfactorily in the lateral position, which is more effective in the maintenance of good respiratory exchange and an adequate blood pressure than is the prone position (see p. 418).

We now recommend this operation as the procedure of choice in all but the most advanced cases of coronary disease. It is absolutely essential to remove the first three thoracic ganglia to prevent residual pain (see Case 6A, below). Our experience has shown that, although it is not ordinarily necessary to remove a greater length of the chain to achieve immediate relief, return of pain may take place with recurrence of sympathetic activity in the arm after a year or two. For this reason we are now resecting the chain from the inferior cervical down through the fourth or fifth thoracic ganglia in the better-risk patients who can tolerate a slightly longer operation with resection of the central ends of two ribs.

In our recent cases we have resorted more and more to surgical excision in preference to paravertebral chemical interruption. Surgery is less likely to be followed by postoperative neuralgia or recovery of afferent conduction, and is a far surer method of interrupting the majority of pain-conducting fibers. At present, with improved methods of intratracheal anesthesia and the more physiological lateral position, we doubt that operation carries a much greater risk of mortality. Injection, although causing somewhat less

TABLE XIV (*Continued*)

Relief of Pain in Severe Angina Pectoris by Upper Thoracic Sympathetic Ganglionectomy

Activity After Operation	*Follow-up Period*	*Cause of Death*	*Pain at Death*
Overactive in business despite painless warning signal. Took no care of himself.	7½ mos.	Cardiac decompensation.	Right side only
Survival period too short to evaluate	12 days.	Post-mortem Luetic occlusion coronary orifices, total on R, 50% on L.	Right side only.
Led active life but suffered partial recurrence after first year	5 yrs.	Probable coronary thrombosis.	Bilateral.
Survival period too short to evaluate.	1 mo	Empyema secondary to postoperative pneumonia.	None
Moderately active life with mild attacks in lower jaw at 15 mos	15 mos.		
Continued practice of medicine with only mild residual pain in lower jaw Partial recurrence of R precordial pain at 5 yrs. coincident with reinnervation of sweat glands. A year later recurrent pain developed on L.	7¾ yrs	Sudden death following day of work with much precordial pain.	Bilateral.
Restricted activity for 7 yrs., but able to drive truck in warm weather	7 yrs	Sudden death at home. Probable coronary thrombosis.	Not known.
Active work as tax investigator at 5 yrs. Little need for nitroglycerine	5 yrs.		
Complete relief of pain and rare episodes of mild tachycardia. Leads normal life.	2 yrs.		
Limited activity but pain free to death.	7 mos.	Probable coronary thrombosis.	None
Convalescence uneventful until sudden death on fifth day	5 days	Post-mortem: Old myocardial scars and recent infarct.	None.
Pain free during a month's postoperative observation at hospital	1 mo		
Remains pain free and much more active.	2 yrs.		
Pain free but has adequate warning signal on exertion.	1 yr.		

TABLE XIV

Relief of Pain in Severe Angina Pectoris by Upper Thoracic Sympathetic Ganglionectomy

Case	*Age*	*Etiology*	*Operation*	*Relief*
1A.* Giuseppe G. MGH # 270150	20	Rheumatic heart disease with aortic and mitral lesions Severe long-lasting attacks of angina pectoris, especially at night.	2/5/29. T1-T2 (L)	Good.
2A.* Charles A. MGH # 301517	29	Syphilitic aortitis and aortic regurgitation, angina pectoris with radiation to both arms	8/19/29. T2-T4 (L)	Good
3A.* Augusta B PH # 20064	60	Arteriosclerotic heart disease with coronary involvement.	10/1/29: T1-T3 (L)	Good.
4A.* Nathan O MGH # 305234	62	Arteriosclerotic heart disease with coronary infarction.	3/19/30: T1-T3 (L)	Good.
5A. Elizabeth P. MGH U-187903 BM	58	Arteriosclerotic and hypertensive heart disease.	7/5/39: T1-T3 (L)	Good.
6A Ella W MGH U-334210 BM	44	Hypertensive heart disease with severe bilateral angina pectoris and drug addiction.	10/22/41 Inf. cerv.-T2 (L) 12/15/41. T1-T3 (R) 4/6/43: T3-T4 (L)	Fair Good. Good.
7A Charles C. U S N Hospital, Chelsea	47	Arteriosclerotic heart disease with angina decubitus and severe right-sided angina pectoris.	4/13/42: T1-T3 (R)	Good.
8A James T. U S N Hospital, Chelsea	44	Arteriosclerotic heart disease with coronary involvement.	6/3/43: T1-T3 (L)	Good.
9A Mabel P MGH U-557903 BM	53	Rheumatic heart with hypertension and coronary infarction Paroxysmal auricular tachycardia with severe left-sided pain	11/4/46: Inf. cerv.-T5 (L)	Good.
10A. Evelyn W MGH U-595030	56	Arteriosclerotic and coronary disease with angina pectoris on L.	11/4/47: Inf. cerv.-T3 (L)	Good
11A. John M. MGH U-601372 BM	63	Arteriosclerotic and coronary heart disease with myocardial infarction.	1/22/48: Inf. cerv.-T4 (L)	Good
12A. Donald M. Cushing V. A. Hospital	57	Arteriosclerotic coronary disease with bilateral angina pectoris	2/4/48. Inf cerv.-T2 (L)	Good.
13A. Muriel N. MGH U-606943 BM	43	Arteriosclerotic coronary disease with angina pectoris on L.	2/16/48: Inf. cerv.-T3 (L)	Good.
14A. Floyd W. MGH U-594142 PH	59	Hypertensive and coronary heart disease Angina pectoris on L.	9/19/49: T1-T2 (L)	Good.

* Drs. W J Mixter and A W. Allen helped with the operations in these patients.

This was accomplished by subsequent resection in two stages of segments of the great occipital and other branches of the superficial cervical plexus, but was followed by only a transitory period of relief. A year and a half later the patient wrote that the first operation "removed completely all pain from the lower chest, over the heart, and in the arm. . . . I can truthfully say that in spite of the fact that the last two operations have numbed superficial areas, they have not prevented the recurrence of the deep pains" in the base of the neck, chin, and posterior scalp.

Anginal references to the jaw, head, and neck are presumably conducted centrally in the vagus and propagated by some unknown reflex mechanism.* That it can be treated by interruption of regional somatic nerves has been discovered by Lindgren and Olivecrona (1947), who cite several examples of relief of residual lower-jaw radiation by alcohol injection of the mandibular nerve.

The following case proves that there is no need to remove additional ganglia above or below the three upper thoracic in order to interrupt pain conduction from the heart. Such a minimal gap, however, may be bridged by regenerating fibers. In the present instance this was clearly shown by the fact that anginal attacks again became somewhat painful on the right side coincident with the return of sweating to her arm and face. Furthermore, the persistence of low pain on the left when all the ganglia between the middle cervical and second thoracic had been removed, and its disappearance after further resection of T3 and T4, proves the importance of lower thoracic cardiac nerves.

Case 6A. Dr. E. W., 44. Hypertensive heart disease with bilateral angina pectoris and morphine addiction.

This woman physician came from a family predisposed to cardiovascular disease. She suffered a coronary occlusion in 1939 and thereafter developed frequent attacks of crushing pain in the precordium with radiation to both arms. Nitroglycerine would abort but failed to relieve the attacks, for which she had taken opiates and developed a definite addiction to the drug. Examination revealed a nervous, high-strung woman who was suffering severely from insomnia and pain, so that she had been taking increasing doses of Dilaudid Hydrochloride and Nembutal over the last two months. Her heart was normal as to size and sounds. Blood pressure was 160/110. The electrocardiogram showed evidence of slight left ventricular strain (moderate left axis deviation). It was believed that she would have to be given complete relief in order to lessen her nervousness and eliminate her drug addiction, so for this reason, and with her agreement, a bilateral sympathectomy in two stages was planned

10/22/41: Supraclavicular approach with resection of middle and inferior cervical with the upper two thoracic sympathetic ganglia on left side. After

* Kinsella (1948) has pointed out the interesting analogy that forehead pain, which many people notice after swallowing ice cream, is likewise a reflex mechanism propagated over an afferent vagal arc.

his health, drinking excessively, and keeping late hours, for the next eight months. He was then forced to re-enter the hospital on account of progressive dyspnea and decompensation. On the third day he developed a fatal coronary occlusion, which was observed from its onset. The remarkable feature of this attack was the distribution of his pain, which was confined entirely to the right side of the precordium and stopped exactly at the mid-line. Post-mortem examination could not be obtained.

The second case history illustrates the difficulties which may be encountered by peculiar reference of pain to the head. The typical anginal pain in the chest and arm was relieved by resection of the inferior cervical and upper thoracic ganglia, but the unusual radiation to the upper cervical dermatomes was not interrupted either by resection of the superior cervical ganglion or by subsequent resection of the branches of the superior cervical plexus.

Case 5A. Mrs. Elizabeth P., 58, BM #187903. Arteriosclerotic and hypertensive heart disease with angina pectoris.

Mrs. P. had an unusual hereditary background of degenerative vascular disease. She herself had had a high-grade hypertension for the past twelve years without complications. For the past three years she had suffered from angina pectoris. The attacks, which were entirely localized to the left side, involved the precordium and arm in the usual manner; in addition, pain radiated to the forehead, where it was felt behind the eye, to the upper and lower jaws, and also to the neck and posterior scalp. Before entering this hospital she had been treated by rest in bed for several months without relief.

The patient was an intelligent and most co-operative woman of slender build. Physical examination showed tortuous radial arteries and a blood pressure of 270/130. The heart was just demonstrably enlarged and there were no signs of congestive failure By X ray, the left ventricle was slightly enlarged and the aortic arch tortuous The electrocardiogram was not quite normal but showed fair coronary T waves.

5/10/39: Resection of the left inferior cervical, first and second thoracic sympathetic ganglia.

The resection, made through the supraclavicular approach, was followed by an uneventful convalescence. The attacks of precordial and arm pain were relieved, but she continued to feel pain radiating to her neck, scalp, and face.

7/5/39: Resection of the left superior cervical ganglion.

Following this operation, which divided some of the branches of the superficial cervical plexus, the skin of her neck was at first anesthetic. During this period she had no real pain, but noticed clutching sensations in her throat and some discomfort in the left side of her face on overexertion. As cutaneous sensation in her neck recovered, pain again recurred in this area and became particularly troublesome in the left occipital area. Remembering that she had experienced relief during the period of cutaneous anesthesia, it seemed logical to try the effect of permanent denervation of the area to which this unusual pain was referred.

pain-conducting fibers can reduce the initial value of upper thoracic sympathectomy. On analyzing the late results in White's 7 patients who survived from one to seven years, we find that 4 remained free of painful attacks. Two (Cases 5A and 6A) continued to have much milder discomfort referred to the neck and jaw. In addition, the latter began to have recurrent precordial and arm pain after five years when the nerve supply to the sweat glands in her arms regenerated, and a similar recurrence appeared in Case 3A at the end of a year.

Similar late analysis of Smithwick's 65 cases, of which 54 have survived from one to four years, shows that a third remain entirely free of pain in their attacks, half are free of characteristic angina in the arm and precordium, but have some pain referred to the neck or upper abdominal region, and a sixth are no better. Seven per cent died in hospital and another 10 per cent succumbed in the course of the period of follow-up.

The largest series of thoracic sympathectomies has been reported from Stockholm by Lindgren (1950). In this detailed medical study the author reports the results of 80 operations by Olivecrona and 25 by Sjöqvist. The operative mortality in these two series was 7.5 per cent and 12 per cent. What appears to be an adequate removal of the upper thoracic sympathetic ganglia (inferior cervical through T3 or T4) was performed in every case by the anterior supraclavicular approach. In the 74 survivors of Olivecrona's 80 operations, alleviation of pain referred to the arms was complete "in practically 100 per cent" while precordial pain "was abolished or considerably diminished in 80 per cent." The results in Sjöqvist's series were substantially the same. The favorable effect of operation was vitiated in a small proportion of cases by postoperative neuralgia or by increasing cardiac decompensation. The incidence of spreading radiation to the neck and jaw (40 per cent) is greater than in White's and Smithwick's statistics. Spread of pain to the lower chest and abdomen, after precordial and brachial angina has been interrupted, has been a troublesome complication in a number of Smithwick's cases but has not been observed in these other series. The report of Lindgren is by far the most detailed medical investigation of surgical treatment of angina pectoris that has been published. It should be read by all who are interested in this problem, as it contains complete details of the effect of denervation on heart size and functional capacity, response to hypoxemia and exercise tolerance tests, electrocardiographic changes, and comparisons of the course of the disease in cases treated surgically with corresponding medical controls.

In comparing the results of upper thoracic ganglionectomy with section of the corresponding spinal roots, it is worth pointing out that in the 29 cases listed in Table XV there have been no recurrences of precordial or arm

this operation there was relief of all pain on the left side except for a slight residual distress under her breast, but with the continued right-sided attacks her convalescence was complicated by psychic changes secondary to her drug addiction.

12/5/41: Posterior approach through second rib with removal of upper three thoracic ganglia on right side. Convalescence after the second operation in the absence of painful anginal attacks was more satisfactory. Her warning signal now consisted of episodes of painless dyspnea. These attacks, which were controlled by nitroglycerine, diminished in number from a preoperative frequency of up to forty a day to between six and eight. After a period of two months' psychiatric rehabilitation, she returned to her home and practice. She was then able to continue office work for a period of seven months, when she had what appeared to be another coronary occlusion. Thereafter she again began to complain of pain low in the left precordium, owing to our failure to resect the third thoracic ganglion. She was readmitted at her own request to complete the denervation of the left side of her heart.

4/6/43: Resection of third and fourth thoracic ganglia on left through third rib approach. An additional 4 cm of the paravertebral chain was removed, including the dural clips applied to the distal stump at the previous intervention. Convalescence was uneventful, and nursing care was far less difficult than at her former admission. Fifteen months later she reported that she had no precordial pain, but infrequent warning signals on overexertion. These consisted of "a slight, but really indescribable sensation in the chest where the old bouts of pain used to be" and some mild but definite pain referred to her neck and lower jaw. "I am more comfortable than I have been in six years. Walking is out, but I can drive without difficulty. . . . Following my doctor's advice, I practice about three hours daily. . . . Last electrocardiogram is not appreciably changed"

Five years after her initial operation, she reported that she never had any precordial or arm pain, but that on overexertion she was "brought up shortly by pain in the neck and jaw. This as a rule is quite bearable and passes in a couple of minutes. . . . I put in an average of six very busy hours daily in medical work. . . . I have noticed during the last few months that when I have an occasional severe attack there is a slight crushing in the chest on the right side. Shortly after noticing this for the first time I observed that such attacks were accompanied with some perspiration of the upper half of the right side of the face and slight moisture of the right palm. . . . In 1941 I felt that I had reached the extreme limit of my endurance and now I am again living a full life."

This gallant woman continued to practice medicine until her sudden death from coronary thrombosis in July, 1949, nearly eight years after her first sympathectomy. During this last year she had suffered another infarction in the spring and complained a good deal of pain on exertion in the chest and both arms. This was never as severe as before sympathectomy, but it shows that in time afferent fibers can regenerate even after extensive ganglionectomy.

It is evident from the last two case histories that spread of pain to areas outside the characteristic zone of reference or subsequent regeneration of

Brief case histories of our patient and the one treated by us and Dr. Ray are given below.

Dr. L., 51. Arteriosclerotic heart disease with coronary occlusion. This prominent physician was referred to us by Dr. David Barr of New York. He was a man of outstanding physical and mental energy who had developed mild substernal oppression in 1929. In spite of this he had continued underwater swimming, skiing, and mountain climbing, as well as carrying on a strenuous practice of medicine. In the spring of 1941 he suffered a mild coronary infarction. From then on he did not slacken his work, but took from eight to twenty nitroglycerine tablets a day with large doses of aminophylline, and suffered pain on less exertion. On arrival in Boston, he was exhausted and was having up to eight attacks by day and five by night, associated with dreams that he was surrounded by the enemy or about to miss a boat and having to run for it. He experienced pain on both sides of the precordium, with occasional radiation to the right as well as the left arm. Physical examination showed a stocky and well-muscled man of middle age without cardiac enlargement or murmur. There was no dyspnea or other evidence of cardiac failure, and his electrocardiogram gave no evidence of recent myocardial infarction. There was a suggestion of calcification in his aortic arch. Blood pressure was recorded as 130/80. The Wassermann reaction was negative, and X ray revealed no evidence of gall-bladder disease, but he had a small hiatus hernia. It was the opinion of the medical department that this was not the cause of his pain.

Because of his good general condition surgical denervation of the heart was recommended in preference to injection of alcohol, but the patient elected the latter. Paravertebral injection of procaine followed by alcohol was carried out on the left side on 3/10/42. The early results were excellent, as the patient had little discomfort and was relieved of all his anginal pain, but three weeks later, while recuperating at the New York Hospital, he developed a severe neuralgia in the left chest. With this he noticed a return of anginal pain on the uninjected right side. Two months later the neuralgia was subsiding when Dr. Bronson Ray carried out a bilateral section of the upper four thoracic posterior spinal roots. After this all vestiges of intercostal irritation disappeared, as well as his residual right-sided angina. He continued to observe an adequate warning signal on overexertion, which consisted of a sense of painless constriction under his upper sternum. He then returned to his home and to his medical work.

The excellent all-around result which followed radical surgery has continued. In a letter written in June, 1946, he stated that he had never at any time experienced pain in his chest. There was only a mild sense of constriction there and also a sense of actual pain referred to his jaw. Unusual reference of pain to this region has been commented on above. Fortunately it always went away with nitroglycerine and, as it prevented overactivity, he felt that it had a definite beneficial value. His electrocardiogram showed a low T wave in the first lead and the presence of ventricular premature beats. He stated that he usually left his house for the hospital at eight in the morning and returned

pain. It is a well-known fact that sensory roots cut within the meninges can never regenerate. There is, however, no reason why spread of pain to the neck and jaw should not take place, and this has occurred in the two patients whose case histories are summarized above.

The fact that regeneration and late recurrence of precordial and arm pain may occasionally occur at intervals of a year or more after sympathectomy makes rhizotomy the operation of choice in the most favorable risks. Upper thoracic ganglionectomy is a less formidable procedure in cases of coronary disease and should be used where long survival is not expected. In the rare case where late recurrence does occur and requires further surgery after ganglionectomy or paravertebral block, root section can be done. When the patient is too poor a risk for open operation, he can still be helped a great deal by chemical block.

Posterior Rhizotomy. Resection of the upper four thoracic posterior spinal roots should interrupt the cardiac sensory fibers with certainty and is a standard procedure in which all neurosurgeons are experienced. Since this operation is more time-consuming, we have only resorted to it in a single unusually good risk patient with bilateral pain and have had the opportunity to follow another extremely instructive case in whom Dr. Bronson Ray performed this operation after one of us had relieved his *anginal attacks unilaterally, but with a complicating severe postinjection* neuralgia. Despite our limited experience we consider this operation the best procedure for treating the good-risk patients with bilateral pain, as it is the only method that allows a complete sensory denervation to be carried out in one stage. Furthermore, it is the most effective way to ensure against regeneration of sensory fibers. We know of no late return of characteristic anginal pain in the precordium and arm.

Results in 30 cases that have been reported to us have been uniformly successful. The mortality rate has been 10 per cent (Table XV).

TABLE XV
Relief of Pain in Severe Angina Pectoris by Upper Thoracic Posterior Rhizotomy (T1 to T4 or T5)

Surgeon	*Cases*	*Deaths*	*Results*
L. Davis, Chicago (1933)	1	0	Complete relief at 4 yr
W. V. Cone, Montreal (personal communication)	1	0	Complete relief
F. C. Grant, Philadelphia (personal communication)	5	1	Residual subclavian pain in 1
H. Haven, Seattle (1942)	5	1	Complete relief at 4 to 10 yr
W. G. Crutchfield, Charlottesville (personal communication)	6	0	Complete relief
B. S Ray, New York (personal communication)	11	1	Complete relief
Totals	29	3	

so treated (White and Bland, 1948) is by far the largest that has been reported. Only 3 have been added since the war, because we have come to realize that surgical exposure and resection of the ganglia or the posterior spinal roots carries little greater risk when carried out under modern intratracheal anesthesia and in the lateral position. At present we are therefore reserving injection for the most advanced cases of coronary disease with angina decubitus, syphilis of the aortic arch which critically narrows the orifices of the coronary arteries, rheumatic fever with aortic regurgitation and threatened cardiac failure, and the very old who cannot be kept in bed. It seems most unlikely that Case 39B, for example, who was completely freed of his exhausting attacks of angina decubitus, could have survived ganglionectomy in view of the fact that he died six months later after a gall-bladder operation. Nevertheless, it is fair to say that over half the patients who were treated by injection before the war could now be handled even more effectively by surgery.

The technique of paravertebral injection has been described by White (1940*B*), and the added improvement of inserting the needles under X-ray control has been proposed by White and Gentry (1944). These methods are described in Chapter XIX. In our experience, failure to relieve precordial and arm pain by this method has rarely if ever been encountered in the presence of signs of an effective paralysis of the upper thoracic sympathetic fibers, i.e., vasodilatation and sudomotor paralysis of the upper extremity, and a Horner's sign. While miosis and ptosis are desirable, as they indicate a thorough infiltration of alcohol well up along the lateral border of the first thoracic vertebra, the production of Horner's sign * is not essential for an effective block of the cardiac afferent fibers. The *sine qua non* is a clear-cut paralysis of the nerves to the blood vessels and sweat glands of the face, neck, and upper extremity.

The points of injection, the resultant intercostal anesthesia, and the distribution of the infiltrated solution are shown in Figure 54. The results in these cases are summarized in Table XVI, A. Examination of this table shows that the method is capable of giving excellent early results in 64 per cent of the cases, and of converting the severe forms of angina pectoris into milder types which can easily be controlled by medical measures in another 20 per cent. In 8 per cent pain has not been satisfactorily relieved. In this group the signs of sympathetic nerve paralysis and anesthesia of the intercostal nerves have not been even briefly maintained,

* In this series available records show a clear-cut Horner's sign in less than half the patients injected. Yet all patients who retained a hot, dry hand had lasting relief of cardiac pain. If the hand became moist and cool within the course of a few days, the attacks invariably recurred.

around six, with an occasional afternoon off. "At present I am on the Governor's Hospital Study Commission and the Statehood Committee. I have just finished as president of the County Medical Society and am involved with the . . . dentists on a study of dental decay in relation to diet. Of course, in a business and professional way I am interested in a number of things, but they are part of work." Another follow-up letter written in December, 1950, stated that he was still free of pain and continuing an active practice of medicine.

A second highly successful result has been obtained by a similar operation at the Massachusetts General Hospital in a 57-year-old man who had suffered two attacks of coronary thrombosis in 1939. He was referred for operation by Dr. James Currens of the medical staff after nine months of increasingly severe attacks of angina pectoris, which were occurring six to eight times a day on the slightest exertion. The substernal pain radiated equally to both arms. A left-sided paravertebral alcohol injection undertaken in June, 1948, in which X ray showed that the first thoracic ganglion had been missed, had interrupted the attacks on that side of the chest but not the arm radiation.

On 7/10/48, with the patient under intratracheal ether in the right lateral oblique position, the upper three thoracic laminae were removed, and bilateral posterior rhizotomy was performed from T1 to T4 inclusive. Recovery was uneventful except for the complication of a hematoma, which developed in the incision as a result of postoperative Dicumarol medication and required drainage. We are now convinced that use of this drug is poor judgment in this type of surgery, and we have never used it again.

Over the two years that this patient was followed, he continued to have an adequate warning signal in which his chest felt tense and there was a peculiar sensation in his throat and lower jaw, with slight pain in his teeth. This responded well to nitroglycerine. All precordial and arm pain was relieved, and he returned to work at his roofing business. On December 12, 1950, he suffered a sudden fatal coronary infarction with pain referred only to his jaw. The diagnosis was verified by post-mortem examination.

Paravertebral Alcohol Injection. For the treatment of patients with severe coronary pain who cannot safely be submitted to either a thoracic sympathectomy or a posterior rhizotomy, chemical destruction of the cardiac rami by the paravertebral injection of Mandl (1925*B*) and Swetlow (1926*B*) is a useful substitute. Its value has been recognized by Bérard (1937), Ochsner and DeBakey (1937), Jessen (1938), Levy and Moore (1941), and Perlow (1942). Our experience with this method dates back to 1927, when a patient with medically intractable angina decubitus and exhausted by pain was successfully relieved He lived for six years without further attacks on the left side (see case history below). Up until the time of World War II this method was used from choice in all but a very few cases. The Massachusetts General Hospital series of 75 cases

have maintained their improvement for periods of from one to ten years. One, although able to do light office work, had a return of considerable angina referred to the lower precordium and jaw within two months of his injection. Five others could not be followed, and 6 died within the first year, but the latter remained free of their formerly severe angina over this short period of survival.

After paravertebral alcohol injection the patients can be out of bed on the following day and rarely require hospitalization for over three or four days. Even after injection, however, a certain number of fatalities and complications are bound to occur. The following early complications have been observed in this clinic:

Pleuritic pain has been troublesome in 4 patients within a few hours after the injection. This has appeared as the procaine has been absorbed, and it is surprising that it is not of more frequent occurrence. One or at most two injections of morphine along with chest strapping have given satisfactory relief. Severe pleuritic pain developed during injection in one case. It necessitated large doses of morphine but subsided within six hours.

Pneumonia followed injection in an eighty-five-year-old woman who was dying of coronary infarction. Injection in her case was undertaken at the urgent request of Dr. Paul D. White, because of the unusual intensity of pain, which had not yielded to large doses of opiates.

Pneumothorax has appeared within a few hours after injection in 2 patients. The cause of this is penetration of the pleura and puncture of the lung, so that air contihues to leak from the injured alveoli for a number of hours. In one asthmatic patient aspiration was necessary for the relief of dyspnea.

Although no instance of intrathecal injection has occurred in this series, such accidents with ensuing transverse myelitis have been reported by Molitch and Wilson (1931), Olsen (1941), and Hirschboeck and Gillespie (1942). We have withdrawn spinal fluid on one occasion, and have always worried over the possibility of infiltrating alcohol into the subarachnoid space. The precautions which can be taken to avoid it are listed in Chapter XX.

Another serious early complication is coronary infarction. This has occurred four times in our experience, with fatal results (see section on deaths, below). Similar accidents have resulted in two other patients a few hours before the time set for injection. John Hunter, an illustrious sufferer from anginal attacks, said that his life was in the hands of "any rascal" who made him lose his temper. His sudden death, which took place after an argument at a medical meeting (Home, 1796), bore out

and it has been evident that failure has been due to the technical difficulty of performing a perfect injection.

When these patients were followed for prolonged periods after their discharge from hospital (Table XVI, B), it was found that of the 50

TABLE XVI

Results in the 78 Cases of Medically Intractable Angina Pectoris Treated by Paravertebral Alcohol Injection

A. RESULTS ON DISCHARGE FROM HOSPITAL		
Complete or nearly complete relief of pain	50	64 0%
Reduction of severe attacks to mild form which can be treated satisfactorily by medication	16	20.6%
Unsatisfactory results	6	7.7%
Died within two weeks of injection	6	7.7%
B. RESULTS IN 28 OF THE 50 CASES LISTED ABOVE AS GOOD RESULTS WHICH WERE FOLLOWED OVER PERIODS RANGING FROM ONE TO ELEVEN YEARS		
Enduring good result	18	64 4%
Recurrence of troublesome angina pectoris	10	35.6%
Of the remaining 22:		
Died in under one year	13	
(9 of these remained free of angina to death)		
Lost track of after discharge	9	

listed as effectively relieved 13 had died within a year, 9 without recurrence of pain. It was impossible to keep track of 9 others. Of the remaining 28, approximately two thirds remained free of troublesome angina, the majority surviving for periods of over two and up to eleven years Out of 16 cases in which alcohol injection of the cardiac nerves had led to a reduction in the severity of cardiac pain to a degree where the patients became moderately comfortable on routine medical therapy, 4 are known to

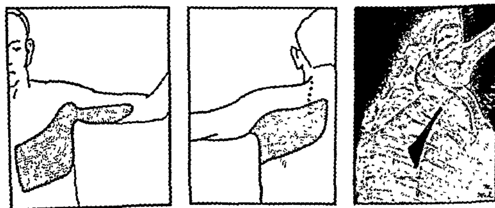


Fig. 54. Points for paravertebral injection in angina pectoris, the resultant area of anesthesia, and distribution of infiltrated Lipidol.

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the truth of this remark. If serious coronary insufficiency in the form of either angina pectoris or coronary thrombosis can be precipitated by anger, it is equally likely to be brought on by emotional strain in the course of paravertebral injection. There is no way to predict this catastrophe, but much can be done to reduce its likelihood by thorough preliminary medication, doing the injection with the patient in his bed, and taking care to reduce pain and emotional stimuli. This complication is also an argument favoring operation under general anesthesia, as ether is a vasodilator drug.

Late complications have been caused by intercostal irritation and neuritis. The sympathetic ganglia lie so close to the intercostal nerves that alcohol infiltrated around the chain cannot help bathing their trunks. They are paralyzed at first, but anesthesia begins to disappear in their anterior divisions within a fortnight. Within a month the intercostal nerves are recovering along their entire length, and with this there is a greater or lesser degree of hyperesthesia of the chest wall, which commonly persists for a number of months. Patients state that pressure of clothing irritates the tender skin, and that there is a burning sensation, with occasional shooting pains In many cases the discomfort is quite bearable and clears up in a month or two. In others (about 10 per cent) it has been a serious problem for several months, but has always disappeared within this time. The pain, at its worst, has caused as much discomfort as the original angina and has required sedation with acetylsalicylic acid or Empirin Compound, barbiturates at night, and occasional doses of codeine. Baking the hypersensitive areas has often been helpful. Nevertheless, with rare exceptions these patients have stated that they would willingly submit to a second injection if their attacks should ever recur. There is, however, no question that intercostal neuralgia constitutes a serious objection to treatment by alcohol injection. In advanced coronary disease its disadvantages are distinctly less than the risk of mortality from operation, but it prevents the application of the method to any but the most severe forms of angina pectoris.

Six patients have died of complications directly attributable to injection. An eighty-five-year-old woman succumbed of complicating bronchopneumonia. A thirty-six-year-old man with rheumatic heart disease and aortic regurgitation died of progressive cardiac decompensation ten days after an uneventful injection. A woman with syphilitic aortitis and 3 men with advanced coronary disease died of coronary infarction precipitated by the injection Death, which occurred in periods ranging from ten minutes to twelve days, was painless except for brief angina on the uninjected side in one case.

That freedom from severe anginal pain may last indefinitely after paravertebral injection with alcohol is surprising, in view of the fact that, after injection of the branches of the trigeminal nerve, facial neuralgia is seldom relieved for more than six months. In this series partial to complete recurrence of pain secondary to nerve regeneration has been observed in a third of the early successful cases after periods of from two and a half months to five years, but, on the other hand, most of the remaining patients are known to have maintained their good result for periods ranging from one to eleven years. It seems remarkable that mere infiltration of alcohol could block the cardiac sensory fibers over such a prolonged period, as we have rarely observed the persistence of a Horner's sign, vasodilatation, or anhidrosis for over a year. Nevertheless, in 4 patients with persistent mild anginal attacks on the uninjected side, there has been continued absence of pain on the injected side for periods ranging from two to six and a half years. In other cases, however, it is likely that the long-lasting results were due, at least in part, to spontaneous development of a competent collateral circulation in the coronary vessels. The reason for this long-lasting paralysis of the cardiac pain fibers is explained by their anatomical structure. The alcohol acts on the delicate rami which unite the sympathetic ganglia with the intercostal nerves dorsally and run ventrally as even more delicate strands to the heart. The rami communicantes are rarely larger than 1 mm in diameter, and the cardiac branches are often no thicker than a hair. They are therefore more easily penetrated by alcohol than are the peripheral nerves, which are thicker and are covered by heavy sheaths of fibrous tissue.

The patients with angina pectoris treated by paravertebral injection have become so numerous that it is not practical to include the details of the entire series, but this has been done in the first 75 cases in the recent report published by White and Bland (1948). A number of brief case histories are given below to illustrate the various forms of cardiac pain which have been treated and some of the more outstanding results.

Case 1B. William M., 54, MGH #280719. Syphilitic aortitis, aortic regurgitation, and angina pectoris.

This patient was the first to be treated by paravertebral alcohol injection. He was a middle-aged carpenter who had had a latent syphilis for many years. Nearly three years prior to admission he had his first attack of angina pectoris, and the pains were soon recurring three to four times a day. Syphilitic heart disease was diagnosed in the cardiac clinic. He was there discovered to have marked hypertrophy and dilatation of the left side of the heart with widening of the aortic arch. There was a very loud aortic diastolic murmur, in addition to a moderate aortic systolic and mitral systolic and diastolic murmurs of the Austin Flint

type. His pulse was of the Corrigan type and blood pressure was 170/35. An electrocardiogram showed inverted T waves in the first and second leads, with left axis deviation.

The patient was admitted to the hospital, where he was kept in bed on medical treatment for over six weeks. During this period his angina increased in both severity and frequency. The most troublesome feature of his attacks was that they came for the most part at night, so that he became exhausted from lack of sleep. As a result the patient and his physicians finally realized that he would die of exhaustion unless relief could be obtained by surgical means. This led Dr. P. D. White to urge a trial of paravertebral alcohol injection, which had recently been recommended by Swetlow (1926A, B).

2/12/27: Diagnostic paravertebral procaine block T1 to T5 (left) resulted in freedom from his attacks for thirty-six hours, but not for the long period described by Mandl (1925A, B).

2/21/27: Paravertebral alcohol injection T1 to T5 (left). The injection was performed without complication and gave the characteristic chest wall anesthesia, but without Horner's sign. He reacted differently from all our other patients, in that he noted postoperative attacks of decreasing frequency for two weeks, from which time he had no attacks on his left side. He was able to return home and lead a quiet life in comfort.

A year later milder attacks were recurring in his right arm and chest wall. An attempt was made to stop these by a right-sided injection by another surgeon, but this block and another later attempt were unsuccessful. He was then followed in the out-patient clinic and remained altogether free of left-sided pain and without too great discomfort on the right, where the attacks could be relieved by nitroglycerine. Finally, in 1933 cardiac failure developed from which he died. No autopsy was performed. The relief of his unbearably severe left-sided angina pectoris had lasted over six years.

Case 29B. Dr. W. N., 58, BM #9647. Arteriosclerotic heart disease, coronary occlusion, and angina pectoris.

A physician, who had enjoyed excellent health, began to notice precordial pain on exertion at the age of 43. Two years later he had a coronary infarct, followed by an embolus to his popliteal artery. He was incapacitated for three months, but he recovered sufficiently to be able to return to his practice. During the past eleven years he had been fairly active, but had suffered from frequent attacks of angina pectoris. The pain was substernal and radiated to the left precordium and arm. He obtained quick relief from nitroglycerine until four months prior to his admission, but at that time he had a series of unusually severe attacks lasting one to two hours and requiring morphine for relief. Three days before entry one of these attacks lasted four hours. As all medical measures had failed, paravertebral injection was recommended by Dr. P. D. White. The patient's father had died of coronary thrombosis and his mother of arteriosclerosis. His own past history was not pertinent to his present illness.

Physical examination was not remarkable except for his cardiovascular system. There was no evidence of congestive failure. His heart measurements showed that his apex was 9 cm to the left of his sternum and just outside the

mid-clavicular line. The blood pressure was 150/90. An X ray of his heart demonstrated no abnormality except a tortuous aorta. The electrocardiogram showed a normal rhythm, rate 75, left axis deviation, and diphasic T_1.

4/25/33: Left paravertebral procaine-alcohol injection, T1 to T4. The patient complained of very little discomfort from this procedure. He developed a striking vasodilatation of his left hand and cessation of perspiration, as well as a Horner's sign. The postoperative X ray showed a slight degree of pneumothorax, but this subsided within a few days. A letter received six weeks later reported that he had again returned to his practice and was totally free from attacks. Furthermore, he had no discomfort in the anesthetic area in his chest. During the next fourteen months he carried on moderately active work and remained free of left-sided angina pectoris. He had, however, noticed the onset of pain in his right precordium. At first this had been a useful warning signal, but lately it had become increasingly severe. He was so pleased with the result of his left-sided injection that he re-entered the hospital on 6/12/34 for a similar procedure on the right. On the day of his admission he had attended his daughter's graduation exercises from college, and noticed an unusual amount of right-sided pain as he walked to his room. At midnight he was awakened by terrific pain in his right chest, which caused him to go into collapse; there was only a slight sense of oppression on his left side. During the course of this attack his blood pressure fell, respirations became labored, and he died three hours later.

Autopsy: There was nothing remarkable outside the heart, which showed diffuse calcification and areas of occlusion and recanalization in both coronary arteries. There was a moderate degree of aortitis and marked scarring of the left ventricle and septum. No recent thrombus could be made out. The only evidence of the old alcohol injection was thickening of the pleura in the region of the second and third thoracic ganglia.

Case 39B. J.H.L., 63. Arteriosclerotic heart disease with angina pectoris. This patient was seen in the University Hospital, Charlottesville, Va., in consultation with Drs. A. D. Hart and J. E. Wood. His angina pectoris dated back over an eight-year period, but he was able to get along quite comfortably on medical treatment until the spring of 1935. At that time he had a fairly severe attack of coronary thrombosis, from which he made a slow convalescence. His anginal attacks then became a matter of great difficulty, increasing in frequency up to thirty or forty attacks a day. The attacks radiated to both arms and were especially severe at night. He had been in the hospital for over a month while unsuccessful attempts were made to give him rest at night with oxygen inhalations and opiates.

The patient was obese. He had moderate peripheral arteriosclerosis and a blood pressure of 170/95. The cardiac dullness could not be determined with great accuracy, but it was thought that the heart was enlarged. Its sounds were of fair quality and there were no murmurs.

As it was felt that the patient could not long survive the exhaustion brought on by his loss of sleep, it was hoped that bilateral alcohol injection might give him much-needed relief.

10/8/35: Paravertebral alcohol injection, T1 to T4 (left).

10/9/35: Paravertebral alcohol injection, T1 to T4 (right).

The patient came through both injections with a minimum of discomfort and proceeded to recover in a way that exceeded all our hopes. He never had another attack of cardiac pain, but continued to have a satisfactory warning signal, which consisted of a sense of oppression in his suprasternal notch. With adequate sleep he was soon able to leave the hospital, and in a remarkably short time he resumed mild activities in his store. When seen six months later he remained at work and free of pain. Unfortunately, ten months after injection, he had a flare-up of an old subacute cholecystitis, for which his medical advisers were not consulted. Operation, which was performed at another hospital, resulted in an early death from congestive failure.

Case 35B. Evelyn C., 26, MGH #337315. Rheumatic heart disease with aortic stenosis and angina pectoris. (This patient has in greater detail been reported by Bland and White, 1936.)

The patient had rheumatic heart disease with marked cardiac enlargement, free aortic regurgitation with a blood pressure of 170/50, mitral stenosis and regurgitation, and angina pectoris decubitus. Severe rheumatic fever and heart disease began at the age of 9 years. A recrudescence of rheumatic fever occurred at the age of 16, requiring hospitalization for twelve months. She subsequently did well and remained free of symptoms except for moderate exertional dyspnea and palpitation until December, 1933, when, at the age of 26, she re-entered the hospital with another recrudescence of rheumatic fever. While at rest in bed she began to have severe angina pectoris Her attacks were characterized by paroxysmal discomfort owing both to pain and to associated circulatory phenomena. The sequence of events began with consciousness of forceful regular heart action and a sense of throbbing in the throat, accompanied by an increase in the pulse rate from a resting level of 90 up to 130 or 140 per minute. In one to two minutes an aching precordial pain appeared, rapidly becoming severe and spreading upward in the chest and down the left arm as far as the wrist. Respiratory discomfort and a sense of choking were usually present, as well as profuse sweating and generalized flushing of the skin. A blood-pressure determination was not made during an attack Occasionally, dyspnea and palpitation occurred without pain, but never the reverse. Although precipitated by emotion or exertion, the attacks most frequently occurred without provocation, especially during the night. The severe anginal pain was usually superimposed upon a less intense precordial aching sensation similar to that frequently described by patients during active rheumatic fever. Nitroglycerine gave partial relief, but it was this latter component of the patient's discomfort which remained uninfluenced by the drug and for which morphia was required frequently.

5/31/34: Paravertebral alcohol injection, T1 to T4 (left).

There resulted a well-marked Horner's syndrome, a transient partial anesthesia over the left chest anteriorly, and a variable paresthesia over the left upper back and down the inner aspect of the left arm. This was followed by complete relief from the anginal pain during frequent subsequent attacks, the presence of which was made known by a tightening sensation in the throat and a persistence of the accompanying palpitation, respiratory dis-

comfort, and generalized flushing of the skin. However, another important element in addition to the pain had been dispelled; namely, the fear of an impending attack. It is of considerable interest that the precordial ache, which previously had not responded to nitroglycerine, persisted off and on in a modified form, but on the whole was less severe and less frequent. This component appeared to be directly related to the active rheumatic disease and subsequently entirely disappeared. The patient was seen at frequent intervals, and was examined in June, 1936, two years after the injection. She was then in good condition and was free from clinical and laboratory evidence of active rheumatic infection. There remained a slight residual Horner's syndrome and a vague sense of numbness to touch over the precordial area, with slight paresthesia along the inner aspect of the left upper arm. She led a quiet life and was able to do light household work. About once a week she had to pause for a few minutes because of tightening in the throat and thumping of her heart, but this was now always related to unusual exertion or excitement.

Nearly four years after the injection the patient developed subacute bacterial endocarditis, from which she died. She remained free of her old anginal attacks throughout.

Case 51B. Mrs. Amelia F., 66. Hypertensive heart disease and angina pectoris.

This woman, referred by Dr. Robert L. Levy, had suffered from attacks of left-sided angina pectoris for ten years. These became much worse following an infarction in 1936, so that she was restricted to her room and required morphine for relief of the pains, which failed to respond to nitroglycerine or codeine. These attacks often occurred in bed and she was losing sleep and weight. The electrocardiogram had shown progressive changes with inversion of T_1 and T_2 and upright T_4. There were left ventricular preponderance and a slow rate from 40 to 60.

4/17/37: Left paravertebral injection, T1 to T4, was performed in her room. She was able to be up on the following day and had a minimal degree of neuralgia during the next few weeks. With the disappearance of her anginal attacks she no longer suffered from insomnia, and her weight and cardiac reserve were regained rapidly.

Nine years later Dr. Levy reports: "She is now 75 years old. . . . In her case the injection of alcohol remade her entire life. She has been completely free from cardiac discomfort for several years. She is very active and is a director of the . . . Home for Old People. She goes out to dinner two or three times a week and plays bridge frequently. She goes to the theatre and the movies. She is happy and in remarkably good health for a woman of her age. The last electrocardiogram was made on April 14, 1943. At that time there was a well-marked sinus arrhythmia and left axis deviation. There were no changes indicating myocardial damage. The blood pressure was 154/86. It is my opinion that the injection prolonged this patient's life, although this point would be difficult to prove."

The improvement in the second electrocardiogram reported by Dr. Levy is noteworthy.

Eleven years after her injection, she continued to lead an essentially normal life for a woman of her years.

Case 61B. Reginald F., 46. Arteriosclerotic heart disease with coronary occlusion and angina pectoris.

This retired army officer was referred to us by Dr. H. M. Marvin of New Haven. Since World War I he had had "soldier's heart" with easy fatigue, dyspnea, and palpitation. Seven months before he came to the hospital he had a sudden attack of precordial pain, with radiation to both arms, which required morphine for relief. Three months prior to admission he had another severe attack of precordial pain. He then began to suffer frequent and intense attacks of bilateral angina pectoris. As this patient was a high-strung, strenuous man, he reacted poorly to inactivity and could not be controlled by medication. His heart was not enlarged, sounds were of fair quality, no murmurs, rate and rhythm were normal. Electrocardiogram showed inverted T waves in leads 2 and 3, with a normal chest lead.

10/27/38 and 10/29/38: Left and right-sided paravertebral injection of alcohol. These were followed by more than the usual degree of neuralgia, as had been anticipated from his nervous make-up, but the thoracic discomfort subsided in a little over a month. He then returned to Bermuda. Six months later he reported that he was "working and exercising almost normally." Two years after injection he was able to pass his army medical examination. On nervous or physical strain he experienced a warning signal which consisted of "slight congestion on the sides of the throat or aching in the left arm like rheumatism." In January, 1941, his local doctor reported him to be "absolutely well in all respects." At the onset of the war he tried to return to active service and would have been reinstated in his commission had it not been for the past history of angina pectoris. In June, 1945, he was reported as lost at sea in a small sailboat off Bermuda.

When allowance is made for the type of patient dealt with, it is evident that paravertebral alcohol injection, in comparison with surgical denervation, carries the lesser risk without too great a sacrifice in effective results. However, injection must be performed with the most scrupulous technique in order to place the alcohol with sufficient accuracy to ensure destruction of the sympathetic rami and the cardiac nerves. As mentioned below, animal experiments have shown that 5 cc of alcohol produce an *area of necrosis not much over 1 cm in diameter. Observations* made during two post-mortem examinations have shown that this applies to man. The infiltration of alcohol must therefore be far more exact than when procaine is used, as this drug diffuses so much more widely through the retropleural tissues. For this reason injection should always be carried out with roentgenographic control of the insertion of the needles. It is always evident when the alcohol has been correctly placed because of the unequivocal signs of paralysis of the upper thoracic sympathetic rami.

When these persist, pain is as effectively relieved as though the same structures had been resected, but the effectiveness of the block is not so certain to endure.

In summarizing our experiences with the neurosurgical treatment of the most severe forms of cardiac pain, we wish to re-emphasize that surgical resection of the upper thoracic ganglia or posterior rhizotomy of the corresponding spinal nerves are unquestionably better methods of dealing with cardiac pain than paravertebral alcohol injection, provided the patient can tolerate an operation. Resection of the sympathetic ganglia may also cause neuralgia, but this is much less of a problem than after alcohol injection, and destruction of cardiac afferent pathways is much more certain. Many of those suffering the most severe pains from angina pectoris, however, are impossible risks for surgery, and even in the most carefully selected group there will be an occasional fatality.

In choosing between surgical and chemical denervation, much depends on the training of the surgeon. Cutting the posterior spinal roots and also thoracic ganglionectomy fall within the routine operations performed by the neurosurgeon. But the technique of paravertebral alcohol injection is more difficult to learn and requires frequent repetition in order to perfect it. Satisfactory results can be obtained in no other way, nor can really serious complications be avoided. Mastery of the technique is well worth the effort required, because it enables a number of otherwise hopeless patients to gain relief from their pain.

In conclusion, we believe it can be stated that the sensory pathways which carry pain from the heart have now been established. In the average sufferer from severe angina pectoris, they can be interrupted without any greater risk than that involved in the management of abdominal and pelvic carcinoma in this age group or in general surgical procedures done on patients with arteriosclerotic coronary arteries (Morrison, 1948). The fear that extensive denervation may result in further damage to the heart with coronary disease (Danielopolu, 1949) appears to be quite unfounded. This is also true of Mackenzie's dictum that surgical relief of pain in angina pectoris, if ever achieved, would be dangerous, because the patient would be deprived of his warning signal. Among these 93 patients treated by surgical and chemical denervation we have now followed a large number in whom all sensation of pain has been removed. Yet they always have retained an awareness of their attacks, either from a sense of thoracic oppression without pain or from palpitation or shortness of breath.

Before leaving the subject of cardiac denervation, the recent modifi-

cation in operative procedure recommended by Fauteux (1946) deserves comment. This writer has proposed resection of the cardiac nerves adjacent to the coronary arteries and ligation of the coronary sinus. This operation requires a wide exposure of the heart. Periarterial dissection of the coronary nerves in the beating heart is at best a difficult procedure, and a considerable length must be resected to prevent their regeneration. In addition, there is little evidence that vein ligation will result in an increased collateral blood flow, especially in the presence of arteriosclerotic vessels. In fact, C. S. Beck and Mako (1941), after an experimental investigation of ligation of the coronary vein, concluded that its beneficial effects were probably not great enough to justify its application to patients. Although Fauteux (1946) reported only one fatality in his first series of 5 patients, it must be borne in mind that the operative exposure and manipulation of the heart required to carry it out are substantially the same as in Beck's endeavors to increase myocardial circulation by the application of vascular grafts. In this operation experience has shown the mortality rate to be prohibitive (see below).

While it is our belief that sensory denervation of the heart is the most practical method of dealing with the problem of intractable angina pectoris, several other methods have been tried but have fallen into disuse because of their prohibitive mortality rate or inconstant results. These consist of:

1. Total thyroidectomy. This operation, proposed by Blumgart, Levine, and Berlin (1933), is based on the reduction in work of the heart which results from lowering the basal metabolism. According to Cutler and Hoerr (1941) and Blumgart (1936), the operative mortality is about 9 per cent. Relief from pain is not so consistent as after interruption of the sensory nerves from the heart, as in the Peter Bent Brigham Hospital series only 8 out of 12 patients had a "sustained clinical improvement." In the single example which we have been able to observe, a patient who required further treatment after total thyroidectomy performed at another hospital, angina continued to be severe unless the basal metabolism was allowed to fall to the level of severe myxedema. As total thyroidectomy is just as serious a procedure as sensory denervation, we no longer consider it to be a justifiable procedure in the treatment of angina pectoris.

2. Increase in collateral coronary circulation by vascular grafts: Beck's (1943) method of increasing the myocardial circulation by application of vascular grafts from the intercostal muscles at first seemed to be a valuable suggestion. Continued experience, however, has shown that the mortality rate of 37.8 per cent is prohibitive (Feil, 1943). Furthermore, it is highly questionable whether a muscle which no longer fulfills its normal

function can retain a satisfactory circulation. On this basis O'Shaughnessy's (1937) proposal of utilizing omental grafts seems distinctly more logical, and it is a pity that his studies were cut short by his untimely death at Dunkirk.

Even if the technical difficulties of attaching vascular grafts to the myocardium could be successfully solved, it remains a question if the collateral circulation could be increased rapidly enough to save many of the patients with severe angina pectoris. In the majority of these most critical cases, as we have shown above, it appears that a fairly adequate collateral circulation can develop spontaneously if the patient is relieved even temporarily from the fear and exhaustion connected with recurrent agonizing attacks of pain.

III. Neurosurgical Relief of Pain in Aortic Aneurysm

Most aortic aneurysms are not acutely painful but cause symptoms only through pressure on neighboring structures. At times, however, they may produce intense suffering. In our experience this has been particularly true when the aneurysm is situated in the aortic arch and is expanding upward into the outlet of the thorax. It would be logical to suppose that under these circumstances the pain is caused by pressure on the parietal pleura and the intercostal nerves. In order to test the pathway of pain sensation, one of us (White, 1932) performed diagnostic procaine block in 3 patients with large and intensely painful aneurysms of the aortic arch. The first case was particularly interesting because the pain was referred to the right upper chest, shoulder, neck, and scalp, i.e., over the cervical as well as the highest intercostal nerves (Fig. 55). All pain was relieved for thirty-six hours by paravertebral procaine injection of the first and second thoracic ganglia, although detectable anesthesia of the skin was limited to the axilla. A subsequent injection with 95 per cent alcohol gave the patient complete relief for the remaining three months of his life. In this instance right-sided pain was caused by an aneurysm of the ascending arch of the aorta, whereas in the second and third cases the aneurysms involved the transverse and upper portions of the descending arch and the pain was left-sided. These patients were all given satisfactory relief, which in the case of the longest survivor lasted for five and a half years. Reichert (1934) has relieved the pain from an aneurysm in the lowest portion of the descending arch of the aorta by injecting the second to sixth sympathetic ganglia. Eleven months after injection this patient remained free of pain and had returned to active work. In our second case procaine alone gave effective relief for the remaining three

months of the patient's life. A similar experience has been reported by T. Rasmussen and Farr (1946). In view of this possible long-lasting effect, a single trial with procaine block is desirable in every case.

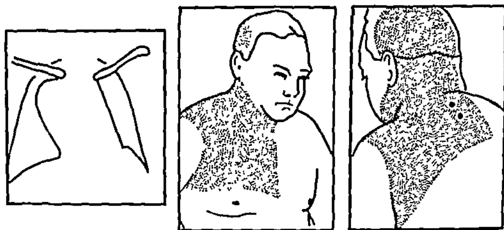


Fig. 55. Aneurysm of ascending arch of aorta.
Stippled area represents region to which pain was referred. The black dots mark the points of insertion of needles for paravertebral injection of upper two thoracic ganglia.

We have recently had a sixty-seven-year-old woman with two aneurysms, in the descending arch and midthoracic aorta, which the surgical consultants felt were not suitable for wiring. She was suffering steady pain and intermittent intense paroxysms which occurred up to twice daily and required Demerol Hydrochloride for relief. The pain was throbbing and radiated from beneath the sternum to the left breast. At the time of the paroxysms her face and neck became cyanosed and she broke out in a drenching sweat. With our recent policy of operating whenever possible in preference to alcohol injection, and because a paravertebral denervation appeared to be unsafe on account of the proximity of the aneurysms, we elected to cut the posterior spinal rootlets. Rhizotomy, performed in the anterolateral position in two stages from T1 to T7 gave complete relief. Instead of her previous unbearable paroxysms she complained only of transitory attacks of dyspnea. Death came suddenly and painlessly seven months later as a result of rupture of the aneurysm.

IV. Operation on the Cardiac Accelerator Nerves in the Cardiac Arrhythmias

Over eighty years ago the following quotation appeared in Edes' book on the physiology of the sympathetic nervous system (1869): "Hyperkinesis cordis, or nervous palpitation of the heart, may be properly re-

garded as a neurosis within the sympathetic; and is undoubtedly an excitation of the nerve centers acting through the various cardiac branches, especially the lower or 'accelerator.'" Beattie, Brow, and Long (1930) showed that asystoles under light chloroform anesthesia were prevented by cutting the sympathetic accelerator fibers. Further experiments by Nahum and Hoff (1935) suggested that many ectopic rhythms are promoted by adrenaline and abnormal activity of the cardiac sympathetic nerves.

Clinical application of this work has shown that upper thoracic sympathectomy or chemical block are effective methods of stopping recurrent bouts of paroxysmal auricular tachycardia and fibrillation. Leriche and Fontaine (1929*A*) reported successful results in 2 cases after bilateral stellate ganglionectomy. One of these maintained a normal rhythm for over four years. Numerous other reports of successful cases are now on record, notably those of Langeron, Desbonnets, and Delvallez (1935); Leibovici, Dinkin, and Wester (1939); and Coleman and Bennett (1938). The first of these articles contains a historical review. To judge from the report by Coleman and Bennett, it would seem that injection of alcohol might be just as effective as actual resection in protecting against repeated bouts of tachycardia. This has unfortunately not been our experience in the cases reported below. We agree with these authors that the simple injection of procaine hydrochloride may be sufficient to break up a single severe attack, but we have not found this to be invariably the case.

Dr. P. D. White and Dr. H. L. Higgins first gave us an opportunity to investigate 2 cases of paroxysmal tachycardia in children; these cases were so severe that they led to periods of congestive failure. With the help of Dr. E. F. Bland and Dr. Sylvester McGinn, the influence of paralyzing the cardiac accelerator nerves was studied by taking electrocardiograms during procaine injection. In one child the heart continued to beat at a rate of over 200; in the other, whose case is summarized below, it was restored to normal rhythm.

Case 1. Paul W., 4, MGH #329222. Paroxysmal auricular tachycardia. Spells of paroxysmal tachycardia began at the age of 2. At first these were infrequent and of short duration, but prior to admission they occurred on an average of once a week, lasting from twenty minutes to two weeks. The patient had had eleven previous admissions to other hospitals. During prolonged attacks he developed congestive heart failure. His condition had not been improved by full digitalization, quinidine, or physostygmine.

6/3/33: Injection of left upper thoracic ganglia with procaine during an attack. Rapid rate persisted.

6/7/33: Similar injection on right side after tachycardia of a week's

duration. Injection was performed while electrocardiograms were being taken (Fig. 56). Within a few minutes there was an extraordinary change in the heart rate, which fell from 210 beats per minute to a normal rhythm of 83. During the transition there were periods of asystole alternating with short intervals of tachycardia.

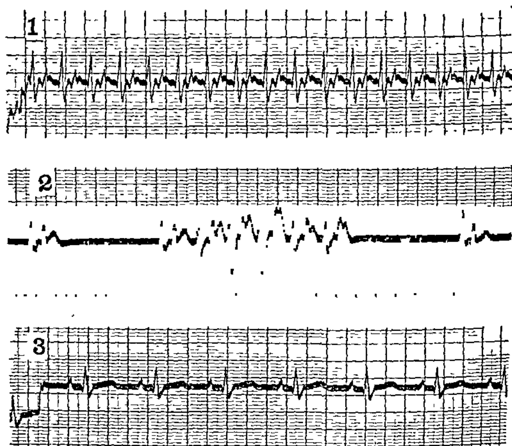


Fig. 56. Paroxysmal tachycardia restored to normal rhythm by injection of right stellate ganglion with procaine and alcohol (Paul W.).

1 Electrocardiogram just before injection. Rate 210. Lead 1. In this and the following records, time intervals separated by the heavier lines = 0 2 seconds.

2. A few minutes after injection. Cardiac standstill up to 1.4 seconds alternating with periods of tachycardia above 200 During this tachycardia and in the isolated beat between the spells of tachycardia, the QRS wave precedes a very high P wave, which suggests an atypical A-V nodal tachycardia Lead 2.

3. Normal rhythm and rate of 83 a half hour after injection Lead 1.

6/19/33: Paravertebral alcohol injection, T1 to T4, under gas-oxygen anesthesia.

The boy remained free of tachycardia for three weeks, then had a very severe attack. He was admitted after two weeks with cardiac decompensation. The signs of complete sympathetic paralysis had disappeared. Reinjection of procaine again stopped the attack.

Two days later the child suddenly died.

Autopsy showed death to be due to a cerebral embolus and hemiplegia. The source of this was a mural thrombus in the left ventricle; otherwise the heart was grossly normal.

From the experience gained in recent years, it is obvious that this child should have had the ganglia resected. Alcohol injection in a young child must be done under a general anesthetic. Under these circumstances it is very difficult to produce a permanent sympathetic paralysis, because evidence of accurate placement of the needles cannot be obtained (see p. 472). Recent experience has also brought out the fact that diagnostic procaine block is not very helpful in picking out the cases of tachycardia that will respond well to sympathectomy. In some of those reported below, paravertebral block has not stopped an attack, whereas the response to ganglionectomy has been satisfactory. Furthermore, false positive results may result through the systemic action of the drug. Mushin and Rendell-Baker (1949) have shown that procaine injected intravenously is a practical method of aborting an acute attack.

The difficulties encountered in obtaining a sufficiently complete chemical block to interrupt the cardiac accelerator fibers permanently are further emphasized in the following case, in which the presence of moderately advanced coronary disease made us hesitate to attempt surgical interruption of the cardiac accelerator fibers. This would not have been the case today.

Case 2. Abigail W., 69, MGH U-96128 BM. Irritable heart with paroxysmal auricular fibrillation, coronary disease, and angina pectoris.

The patient, referred by Dr. P. D. White, was a stout elderly woman, who had noted attacks of rapid, irregular beating of her heart for nearly twenty years. In 1934 these episodes occurred with increasing frequency, and with them she began to suffer from precordial pain with radiation to both arms. Nitroglycerine gave no relief. These attacks lasted from a few hours to several days, but their duration could be reduced by quinidine. This drug, however, caused troublesome intestinal upsets.

On physical examination the patient was found to have generalized arteriosclerosis and a blood pressure of 120/40. The heart was slightly enlarged to the left. During an attack the rate was about 140 and the sounds were very irregular in force and rhythm. There were no signs of congestive failure. Electrocardiogram showed flat T_1 and sagging T_2 and T_3. In lead 4 the T wave was diphasic, with the initial phase inverted.

Bilateral paravertebral injections were performed with alcohol (2/8/36 and 2/20/36) in the hope of stopping both her cardiac pain and her bouts of fibrillation. This result was achieved, but not permanently. A year and nine months later she returned to the hospital. At this time she was able to stop recurrent attacks with five quinidine tablets, but these gave her so much

diarrhea that she requested reinjection. This was again done bilaterally (12/1/37 and 12/4/37) with very little discomfort. Again she experienced relief from both her pain and fibrillation, but this time it lasted for only a month *

This patient illustrates the fact that the cardiac accelerator nerves must usually be interrupted bilaterally in order to put a stop to recurrent attacks of tachycardia. After the first injection on the right, anginal pain was no longer felt on that side, although recurrent bouts of tachycardia continued unchanged. Following the left-sided injection, tachycardia as well as angina attacks were relieved during the period of complete block. Both recurred with return of fiber conduction. Reinjection again put a stop to the attacks, but only for a brief period, as secondary block with alcohol in a zone of scar tissue is rarely effective for long. Permanent relief could have been obtained if the ganglia had been resected. This has been done in the 5 more recent cases, reported in detail by White and Bland (1950). The over-all results of surgical intervention for paroxysmal tachycardia in our 7 cases are summarized in Table XVII.

Examination of this table shows that ganglionectomy must be extensive in order to prevent recurrence of attacks. This has taken place in Case 6, with return of sweating and lowering of electrical resistance of the skin, with a coincident increase in the number and severity of the attacks. In this man with severe congenital cardiac disease, blood pressure fell, on induction of anesthesia, to such an alarming extent that only the upper three thoracic ganglia could be resected. In 3 others operated upon by White, the central ends of both the second and third ribs were excised and the extent of sympathectomy increased to include all the ganglia from the inferior cervical or first thoracic down to the fourth or fifth. These patients have maintained the original reduction in frequency and severity of their attacks, but they have continued to experience asystoles and occasional episodes of tachycardia at times of emotional strain, excessive fatigue, or other illness. None is totally free of tachycardia, but the disease, which was formerly so severe and resistant to medication that the patient was totally disabled, is now no longer a serious problem. All these individuals are able to lead essentially normal lives, with only occasional need for medication. Furthermore, the milder residual attacks, which were formerly resistant to digitalis, ipecac, or quinidine, are now more readily controlled by medication.

After sympathetic ganglionectomy from T1 to T5, inclusive, these patients tend to have a distinct slowing of the cardiac rate both at rest and in

* It has been our experience with reinjection that when alcohol block has once failed, retropleural fibrosis renders ensuing nerve injection increasingly difficult

TABLE XVII

Results of Sympathectomy in Medically Intractable Paroxysmal Tachycardias

Case	*Age*	*History*	*Operation*	*Result*
1. Paul W. MGH # 32922	4	Two years paroxysmal attacks of tachycardia of increasing frequency and severity without other evidence of heart disease Decompensation in prolonged attacks with maximal cardiac rate of over 200.	6/3/33: Diagnostic procaine block T1 to T2 (L). 6/7: Similar block on R. 6/19: Alcohol block T1 to T4 (R). 7/24: Repeated procaine block T1 to T2 (R).	None. Restoration normal heart beat. Free of tachycardia 3 wk, then recurrence. Tachycardia again stopped. 7/26: Cerebral embolus and sudden death.
2. Abigail W. MGH U-8327 BM	69	Mild attacks paroxysmal auricular fibrillation for 20 yr. Then attacks became severe and intractable, with bilateral angina.	2/8/36: Alcohol block T1 to T4 (R). 2/20: Similar block on L. 12/1/37: Alcohol block T1 to T4 (L). 12/4 Similar block on R.	Anginal attacks relieved on R. Residual pain and attacks of tachycardia stopped for a year, then recurrence. Relief for 1 mo, then recurrence.
3. Mabel P. MGH U-551903 BM	53	Rheumatic and hypertensive heart disease, and coronary thrombosis. Attacks of paroxysmal auricular tachycardia (rate 170) for 12 yr with recent angina pectoris (L). Many syncopal attacks.	11/4/46: Sympathetic ganglionectomy T1 to T5 (L).	Rare mild recurrence of tachycardia without angina past 3 yr. Now able to lead normal life.
4. Ethel S. MGH U-565313 BM	39	Paroxysmal auricular tachycardia and flutter fibrillation for 4 yr with otherwise normal heart. Frequent collapse on exertion.	3/4/47. Diagnostic procaine block (bilat.). 5/19: Sympathetic ganglionectomy inferior cervical through T3 (L). 6/3: Similar operation on R.	Injection on L. stopped attack. At 2 yr carries on heavy routine office work. Has occasional mild attacks when overtired.
5. Augustus H. MGH U-533746	53	Paroxysmal auricular tachycardia for 2 yr without other evidence of heart disease. Attacks induced by mild exertion, prevented work as carpenter.	3/20/47: Diagnostic procaine block (R). 3/22: Sympathetic ganglionectomy inferior cervical through T4 (R).	Able to climb 12 flights stairs without difficulty. Rare mild attacks and able to work at 2 yr.
6. Paul B. MGH U-365933	31	Congenital heart disease (cor triloculare) with secondary polycythemia and paroxysmal tachycardia (rate 180).	10/29/47: Sympathetic ganglionectomy T1 to T3 (R) * 11/24/48: Similar operation on L.*	Reduction in severity and frequency of attacks. Patient is still a cardiac invalid, but at end of 1 yr attacks are less frequent and rate rarely exceeds 120.
7. Anna C. MGH U-624616 BM	66	Paroxysmal auricular tachycardia without underlying heart disease. Daily attacks with total incapacity.	7/7/48· Sympathetic ganglionectomy inferior cervical through T4 (R). 7/26. Similar operation on L.	Mild residual attacks once or twice a month for a year, then nearly complete freedom during ensuing 18 mo.

* Only 3 ganglia were resected because the blood pressure fell to shock level on induction of anesthesia at each operation. We feel that this is an inadequate operation and that the ganglionectomy should be carried downward to include at least the fourth thoracic ganglion, preferably the fifth.

response to exercise. This slowing of the heart has been investigated by Smithwick *et al.* (1949) in hypertensive patients where the removal of the sympathetic ganglia has been extended upward to include the accelerator outflow because of excessive elevation in pulse rate. Their findings in 37 individuals, in whom the response to standard exercise tests and other stimuli were studied, indicate that the cardioaccelerator fibers in man leave the sympathetic trunks between the second and the fifth thoracic ganglia bilaterally, although the outflow from the right seems to be somewhat more important than the left. The effect of a unilateral operation on either side, however, is slight in comparison to a bilateral denervation. Following the latter, the resting pulse rates are slower in all patients, particularly in those having more rapid rates originally. In response to exercise the percentage increase in rate is considerably greater before than after operation, although a physiologically effective degree of acceleration is still maintained after denervation This indicates that the residual ability of the heart to accelerate its beat is the result of reduction in vagal tone. No untoward results have followed complete sympathetic denervation of the heart. This procedure is proving useful in the management of hypertensive and normotensive patients having exertional, emotional, or postural tachycardia, as well as in those with the purely paroxysmal variety, which in the past have been a difficult problem for the cardiologist.

V. Operations on the Cardiac Accelerator Nerves for Emotional, Exertional, Postural, and Paroxysmal Tachycardia

From time to time the occasion arises where unusual cardiac acceleration of neurogenic origin presents a real problem. Although rare, these cases have a degree of disability which defies other forms of treatment. In particular, there are patients in whom the response to an emotional stimulus, such as the taking of an examination or public speaking, results in tachycardia of such severity as to be completely incapacitating. In other instances tachycardia in response to ordinary physical exertion may be so severe as to incapacitate these individuals In most instances these two types of tachycardia are not associated with hypertension, but occasionally they may be. A third form which deserves consideration is postural tachycardia associated with hypertension. This will be referred to in Chapter XII. In these cases the average of 5 readings of pulse rate, taken at one-minute intervals during the postural and cold blood-pressure test, reveals that the heart rate in the upright position exceeds that in the horizontal position by 30 beats or more per minute. Under these circumstances, thoracolumbar splanchnicectomy should not be performed. Instead, a subtotal thoracic denervation

should be carried out (Chap. XII). When the problem is one of excessive heart rate not associated with hypertension, such as in the first two instances referred to, bilateral ganglionectomy from T2 to T5, inclusive, will alleviate the disorder. More complete observations on the effect of removing various portions of the thoracic sympathetic chain and ganglia, unilaterally and bilaterally, upon heart rate have been published by Smithwick *et al.* (1949).

CHAPTER XII

Hypertensive Cardiovascular Disease

I. Introduction

Many attempts to modify the course of hypertensive cardiovascular disease by interruption of sympathetic pathways to large portions of the vascular bed have been made during the past twenty-five years. Stimulated by the failure of medical treatment and by the success which has greeted surgical intervention on the sympathetic nervous system in the treatment of peripheral vascular disease, real progress has been made in the evaluation of this form of therapy.

There are many causes of and diseases associated with hypertension in man. Page (1939*A*) has classified and listed some fifty of these under five headings. renal, cerebral, cardiovascular, endocrine, and unknown. The first four groups contain many generally recognized disease entities such as chronic nephritis, chronic pyelonephritis, intracranial tumors, coarctation of the aorta, and tumors of the pituitary or adrenal glands. All of these conditions must be excluded before a diagnosis of essential or malignant hypertension can be made. The latter are the sole members of the fifth or unknown group in Page's classification and are the ones with which we are primarily concerned in this discussion. Numerically, however, this last group is the largest of all. As a cause of death it has been said to exceed cancer in importance E V. Allen and Adson (1940), referring to Barker (1937) and Fahr (1928), estimated that hypertension is from two to three times more deadly than cancer.

Although its etiology is still a mystery, a good deal is known about the natural history of the disease. If patients are divided into four groups according to the severity of the disease at the time the diagnosis is made,* Keith, Wagener, and Barker (1939) have shown that mortality in five to nine years is 40 per cent in the first group, 65 per cent in the second group, 92 per cent in the third group, and 99 per cent in the fourth group. It is fair to state that as yet no form of medical treatment has been shown to alter the progress of the disease to a statistically significant degree. It is now ap-

* These groups (K.W.B. Groups 1 to 4) are described on p 315.

parent that sympathetic ganglionectomy and splanchnicectomy is the first therapeutic measure which has significantly prolonged the life expectancy of patients with hypertensive cardiovascular disease.

Historically, it is of interest that Bright (1827 and 1836) was probably the first physician to recognize the existence of hypertension in man, and did so about seventy-five years before an instrument for measuring blood pressure became available to the medical profession. His deductions were based upon a study of gross pathology in patients dying of dropsy with and without albuminuria. He noted that, at death, patients with dropsy and albuminuria had diseased kidneys of one sort or another, and this condition came to be known as Bright's disease. Albuminuria was regarded as a synonym. In the absence of albuminuria, the kidneys were generally not affected. In patients with Bright's disease a certain number, about 20 per cent, were found to have hypertrophied hearts. The conclusion was reached that "the two most ready solutions appear to be, either that the altered quality of the blood affords irregular and unwonted stimulus to the organ immediately; or, that it so affects the minute and capillary circulation, as to render greater action necessary to force the blood through the distant sub-divisions of the vascular system." It is apparent that this second suggestion contains several important implications: (1) that some humoral agent may exist which (2) causes vasoconstriction and (3) increased peripheral resistance to the flow of blood through the arterioles which (4) results in elevated blood pressure and (5) cardiac hypertrophy because of the increased work of the heart.

With the improvement of the microscope and the development of the microtome about the middle of the last century, further information was obtained concerning abnormalities of the peripheral vessels, particularly the arterioles. It was first discovered that in "hypertensive" patients the walls of the arterioles were thickened because of hypertrophy of the media. This, according to George Johnson (quoted by Gull and Sutton, 1872) was due to the resistance offered by the minute arteries to the passage of blood being forced through them by increased effort of the left ventricle. "The result of this antagonism of forces is that the muscular wall of the arteries and those of the left ventricle of the heart become simultaneously and to an equal degree hypertrophied." Thus widespread pathological changes in the arterioles became recognized and were first regarded as the result of the hypertension, not the cause.

The concept that "hypertension" (cardiac hypertrophy) was caused by increased peripheral resistance owing to a widespread primary vascular disease, in which the kidneys might or might not participate, was advanced

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* These groups (K.W.B. Groups 1 to 4) are described on p. 315.

from further studies of pathological material from living hypertensive patients and from autopsy material. The literature pertaining to these matters is very extensive and has been summarized in recent years in monographs by Goldring and Chasis (1944), H. W. Smith (1939), Page and Corcoran (1945), and White and Smithwick (1941).

Brief comments on some of this evidence seem indicated in order to orient the surgical approach to hypertension in relation to the problem as a whole. Neurogenic hypertension has been developed experimentally in animals. The work of Heymans (1938), who produced severe persistent elevation of blood pressure by denervation of the carotid sinus and section of the aortic depressor nerves, is of particular interest. Following section of these modulator nerves, the resulting hypertension can be abolished by total paravertebral sympathectomy. Acute hypertension induced by increasing intracranial pressure also can be abolished by extensive paravertebral sympathectomy (Freeman and Jeffers, 1940). Such experiments simply serve to confirm the fact that increased central vasoconstrictor outflow can result in hypertension, which can be abolished or modified by peripheral sympathectomy.

The other most important type of experimental hypertension is that which follows partial occlusion of the renal arteries by a metal clamp. This technique was first described by Goldblatt *et al.* (1934) and discussed by him in subsequent communications (Goldblatt, Gross, and Hanzel, 1937; Goldblatt and Wartman, 1937; Goldblatt, 1940). Page (1939*B*) was able to produce a similar form of the disorder by means of silk or Cellophane perinephritis. This so-called "renal" form of hypertension cannot be modified by either preliminary or subsequent sympathectomy, however extensive. This appears to indicate that the nervous system is not implicated in this form of hypertension. It is thought that the most likely explanation is a humoral substance which has been called "angiotonin" by Page (1940) and "hypertensin" by Muñoz *et al.* (1940). It is felt that this is elaborated because of a reduction in the quantity of blood flowing through the kidney, or by an alteration in the nature of renal blood flow, or both. So far, conclusive demonstration of the existence of a humoral vasoconstrictor substance in the blood of either animals or man with chronic hypertension has not been possible. These experiments serve to show that a form of chronic hypertension can be produced which does not appear to depend upon the sympathetic nervous system for its existence. An interesting theoretical discussion of the possible role of the adrenal and pituitary glands in the genesis of hypertension in man has been advanced by Heinbecker (1948).

by Gull and Sutton (1872). As a result of a detailed study of gross and microscopic changes in patients dying of so-called "Bright's disease," they noted that medial hypertrophy was not the only pathological finding, but that other changes also were present. T[illegible] them to contest the then [illegible] (hypertension). They [illegible] appear to us supported by the facts." Among [illegible] facts they mention are: "There is a diseased state characterized by hyaline-fibroid formation in the arterioles and capillaries. . . . The kidneys may be but little if at all affected, whilst the morbid change is far advanced in other organs. . . . The contraction and atrophy of the kidneys are but part and parcel of the general morbid change. . . . It is probable that this morbid change commonly begins in the kidney, but there is evidence of its also beginning primarily in other organs. . . . In the present state of our knowledge, we [illegible] r change to an antecedent chan[illegible] . . . . The kidneys may u[illegible] changes without being attended by the cardiovascular and other lesions characteristic of the condition known as chronic Bright's disease." Thus, the theory that elevated blood pressure could be due to increased peripheral resistance offered by primary vascular disease came into existence.

With the advent of the sphygmomanometer at the turn of the century, clinicians were able to divide hypertensive patients into two groups, those with and those without evidence of renal disease. It gradually became apparent that the latter was by far the larger group. The terms "hyperpiesia" and "essential hypertension" came into existence. It also became apparent that in the early stages of hypertension little evidence of organic disease of the vascular system could be detected. It was noted that the blood pressure of many of the patients was unusually variable. Abnormal responses to various stimuli such as pain, emotion, and particularly cold suggested the participation of the sympathetic nervous system in this disorder. The phenomenon of vascular hyperreactivity was first described by Hines and Brown (1932) and further discussed in subsequent publications by these authors (1933) and by Hines (1937 and 1940).

It was in this way that the three factors which are regarded as of importance in hypertension today, nervous, humoral, and vascular, came to be recognized. Since 1925 a vast amount of evidence has accumulated concerning each of them. This has resulted from studies of experimental hypertension in animals, from clinical investigation of hypertension in man, and

* Gull, W. W., and Sutton, H. G. "On the pathology of the morbid state commonly called chronic Bright's disease with contracted kidney ('arterio-capillary fibrosis')." *Medical-Chirurgical Transactions*, London, 1872, 55: 273–326

From a practical viewpoint, experience has shown that, regardless of whether basal blood-pressure levels are lowered or not following sympathectomy, life expectancy has been increased to a statistically significant degree in the great majority of patients. As the subsequent discussion will indicate, this is thought to be due to other physiological effects of extensive sympathectomy, particularly a marked reduction in or abolition of the sudden elevations of blood pressure which are due to reflex vasoconstriction of the splanchnic bed in normally innervated patients.

II. Physiological Effects of Adequate but Not Excessive Sympathectomy and Splanchnicectomy in Hypertensive Patients

Before turning to a discussion of the actual reported results of the different operations which have been employed in man, one might briefly inquire how splanchnic denervation may affect the course of hypertensive cardiovascular disease in man. With regard to the therapeutic value of sympathectomy and splanchnicectomy, it seems certain that this is the result of a combination of favorable physiological effects. These may be divided into known and presumed effects, as indicated by Table XVIII.

TABLE XVIII

Physiological Effects of Sympathectomy and Splanchnicectomy for Hypertension

1. Known:
a Modification of reflex vasoconstrictor control of blood pressure
b Variable lowering of basal blood-pressure levels
2 Presumed
a Inhibition of reflex secretion of epinephrine
b. Stabilization of blood flow through denervated viscera

Abolition of sudden elevations of blood pressure following stimuli which result in widespread vasoconstriction has been described by Wilkins *et al.* (1948). These workers have shown that, following adequate thoracolumbar splanchnicectomy with bilateral excision of the sympathetic trunks from the eighth thoracic to the first lumbar ganglia, inclusive, together with the splanchnic nerves arising from these segments, reflex elevation of blood pressure caused by vasoconstriction is abolished or greatly reduced. The same effect is noted after total or subtotal thoracic sympathectomy, in which the chains are removed from the inferior cervical or second thoracic to the twelfth thoracic ganglia, inclusive. These three operative procedures are physiologically equivalent in this respect.

It is believed that the abolition of these sharp overshoots of blood pres-

Moritz and Oldt's (1937) further study of pathological material from hypertensive patients dying of some complication of the disorder served to re-emphasize the existence of organic vascular disease, particularly in the renal arterioles. Their observations confirm the accuracy of those of Gull and Sutton (1872) as to the nature of the changes in arterioles. They divided these into three groups—medial hypertrophy, intimal hyalinization, and endothelial hyperplasia. This clearly establishes the fact that medial hypertrophy is not the only change. Moritz and Oldt interpreted these data as lending support to the Goldblatt theory that pre-existing renal arteriolar disease might be the cause of essential and malignant hypertension in man. On the other hand, biopsy material from the kidneys of living patients with long-standing hypertension obtained during the performance of operations upon the sympathetic nervous system was not found to support this theory. In this connection, Castleman and Smithwick (1943 and 1948) found that in about one half of their patients the evidence of renal arteriolar disease was absent, minimal, or mild at most, and inadequate in their opinion to be the sole causative factor. Thus it was shown that pre-existing renal arteriolar disease was not a necessary precursor to the hypertensive state in man (see Figs. 71 to 74). This evidence also suggests that much of the renal vascular disease found at death develops along with or subsequent to the hypertension.

Evidence obtained by quantitative studies of renal blood flow by the clearance technique of H. W. Smith (1939) also tends to make the kidney the victim rather than the cause of so-called "essential hypertension" in man. Other data as well, particularly on the lowering of blood pressure in the majority of surgically treated patients coupled with reversal of existing cardiovascular damage (as judged by favorable changes in eye grounds, electrocardiograms, heart size, and renal function), all tend to suggest that much of the cardiovascular damage is the result rather than the cause of hypertension. This furthermore suggests that the nervous factor is an important one in many hypertensive patients, at least in the early stage. As a consequence, widespread vascular disease, and perhaps a humoral vasoconstrictor substance as well, may result. These latter mechanisms then become limiting factors in the reversal of hypertension following extensive sympathectomy. In their absence, blood-pressure levels may return to normal or near-normal levels. In their presence, only partial reversal can be expected. If either vascular disease or a humoral mechanism offers increased peripheral resistance to blood flow equal to that mediated by the nervous system, then no *significant change in basal blood-pressure levels will follow* sympathectomy, however extensive.

Valsalva maneuver before and after sympathectomy are illustrated. The effect of total sympathectomy is no greater in this respect than that following thoracolumbar or subtotal thoracic sympathectomy as described. These reflex responses may be lessened somewhat after subdiaphragmatic or supradiaphragmatic splanchnicectomy, but they may still be very active; so far, they have never been found to be abolished by either of these procedures.

Lowering of basal blood-pressure levels varies considerably from patient to patient in both magnitude and duration. Most discussions of the value of surgery in the treatment of hypertensive cardiovascular disease have revolved about its effect upon blood-pressure levels. It is now apparent that patients may be improved for years from the viewpoint of the cardiovascular system and relief of symptoms, and may also have their life expectancy increased significantly, when the effect of operation upon blood pressure is but temporary, or even in cases in which the basal levels are never significantly lowered.

Actually, lowering of blood pressure to a significant degree lasting from one to five years has been noted in about 60 per cent of surviving unselected patients treated by thoracolumbar sympathectomy and splanchnicectomy. With the passage of time there is a tendency for the levels to return toward preoperative values, but about 40 per cent * of living patients continue to maintain as low levels during the second as during the first five-year period of observation. This respite, together with the abolition of reflex elevations of blood pressure, which seem to persist even if the basal levels return to or toward the preoperative levels, appears to be sufficient to exert a very significant effect upon the progress of the disorder.

In addition to the known effects of operation, it is highly probable that reflex secretion of epinephrine is abolished. This diminution in adrenal secretion may minimize a possible pituitary-adrenal cortical factor and thereby exert a favorable effect upon the hypertensive state. Stabilization of blood flow through the viscera, with a decrease in the periods of reduced blood flow due to vasoconstriction, probably also results from sympathetic ganglionectomy and splanchnicectomy. This may exert a favorable influence upon the elaboration of pressor substances by viscera in response to periods of ischemia, if such a mechanism actually exists in man. It seems probable that the favorable effect of sympathectomy upon the course of hypertensive cardiovascular disease is the result of a combination of its physiological effects upon the cardiovascular system.

* When late statistics on reduction in blood pressure are based on the total number of patients operated upon, those who have died as well as the survivors, the proportion of favorable results is substantially lower, as has been pointed out by Evelyn *et al.* (1949) (see p. 341).

sure should greatly lessen the mechanical stress and strain on the cardiovascular system, and may be an important factor in slowing the progress or reversing the severity of cardiovascular disease and in increasing life expectancy This favorable effect occurs in all patients subjected to these operations and appears to last for many years. It is independent of any change in basal blood-pressure levels and has to do only with superimposed sudden elevations of pressure above basal levels. This physiological effect is well illustrated by Figure 57, in which the blood-pressure responses to the

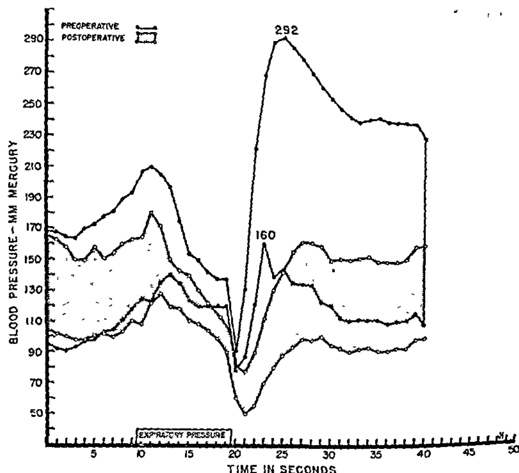


Fig. 57. The Valsalva maneuver performed before and after thoracolumbar sympathectomy and splanchnicectomy.

The blood-pressure levels are comparable in both tests before and during the ten-second period of expiration against a pressure of about 40 mm of mercury In the latter portion of the test, widespread vasoconstriction results in a striking rise in blood pressure to 292/160 a few seconds after the expiratory phase before operation. After operation this phenomenon is abolished It is felt that this physiological effect upon blood pressure, which occurs in all thoroughly denervated patients, is an important factor in reducing the stress and strain upon the cardiovascular system. This effect is not related to changes in basal blood-pressure levels. (Reproduced from Smithwick, R. H. "Continued hypertension. Prognosis for surgically treated patients." *British Medical Journal*, London, 1948, 2: 237–243.)

Valsalva maneuver before and after sympathectomy are illustrated. The effect of total sympathectomy is no greater in this respect than that following thoracolumbar or subtotal thoracic sympathectomy as described. These reflex responses may be lessened somewhat after subdiaphragmatic or supradiaphragmatic splanchnicectomy, but they may still be very active; so far, they have never been found to be abolished by either of these procedures.

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Certain untoward effects are also noted, but, as will be emphasized, these are greatly outweighed by the favorable effects, provided the proper operation is selected for the particular case. Among the unfavorable effects are moderate postural hypotension and tachycardia, excessive perspiration in hot weather, and cooling of undenervated areas in cold weather. If loss of ejaculation is to be avoided in a given case, the lumbar outflow should be preserved on one side. Although the power of erection may be reduced, actual impotence is so rare that it may be disregarded. This infrequent complaint might be due to the nonspecific effect of operation, since it may occur after other major surgical procedures. Erection is known to be a function of the parasympathetic division of the autonomic nervous system, and the sympathetic thoracolumbar division has to do only with ejaculation (see p. 399).

Seventy-five per cent of the patients interviewed five to ten years after operation state that the untoward physiological effects of operation are more than counterbalanced by the favorable effects. The most troublesome problem continues to be a variable degree of postoperative intercostal neuralgia. This persists for a number of weeks in most cases, is rarely absent, and occasionally is very severe. It may last for several months. Increasing experience and facility in performing the operations are making this problem less troublesome. However, it is suspected that the combination of sympathectomy and irritation of peripheral nerves may result in the elaboration of substances which are irritating to somatic nerve endings and cause this particular type of neuralgia In this connection it is of interest that troublesome intercostal neuralgia rarely follows the standard thoracic operations, where the same intercostal incision is used, often with far more trauma to the ribs and structures within the chest, but without removal of the sympathetic trunks. In severe cases peripheral nerve block or subcutaneous procaine infiltration is helpful temporarily, as is also moist heat. Injecting Dolamin * into exposed intercostal nerves at the time of operation appears to be helpful. It is hoped that more effective blocking agents which will produce temporary analgesia without subsequent secondary irritative phenomena will be developed before long.

III. Various Methods, and Their Results, of Treatment of Essential Hypertension by Sympathectomy

According to Peet (1940) the concept of a surgical approach to the problem of hypertension was suggested by Kraus to Brüning and first published

* For the formula of this proprietary compound of ammonium sulfate and benzyl alcohol, see p. 430 (Chap. XVII).

by the latter in 1923 (*A*). The matter was further discussed by Danielopolu (1923). In 1924 Adson performed a periarterial sympathectomy upon the left femoral artery of a patient with malignant hypertension, and in the following year a bilateral lumbar sympathectomy upon another hypertensive patient. These cases were discussed by Rowntree and Adson (1925). In 1930 Pieri (1932*B*) performed a unilateral splanchnic resection for hypertension. In the same year Adson approached the problem by laminectomy and anterior root section and later reported this technique (Adson and Brown, 1934). Craig, in 1934, described a subdiaphragmatic exposure of the splanchnic nerves. The following year Peet (1935*A*) reported his first series of cases in which splanchnicectomy was performed by a supradiaphragmatic approach, the operation which now generally bears his name. This series was begun in November, 1933. Celiac ganglionectomy was later advocated by Crile (1938*A*). Page and Heuer (1935*A*) reported that renal denervation alone had no effect upon the blood-pressure level in one case of essential hypertension, and later (1935*B*) found the same to be true in several cases in which the hypertension was associated with chronic nephritis. Early experience with surgical procedures has also been reported by others (Page and Heuer, 1937*A* and *B;* Page, 1938; Davis and Barker, 1939). Some procedures have been abandoned for various reasons (Allen and Adson, 1940), and the technique of others has been altered. One of us (R. H. S.) has had an extensive experience since 1935 with a number of these operations and has devised a combined supra- and infradiaphragmatic approach, which has been used for twelve years. This technique was called thoracolumbar or lumbodorsal splanchnicectomy and was first described by Smithwick (1940*D*). More recently, total thoracic and total sympathectomy have been described by Grimson (1941).

At the present time four operations are in use: supradiaphragmatic sympathectomy and splanchnicectomy (Peet), the subdiaphragmatic approach (Adson, Craig, and coworkers), thoracolumbar sympathectomy and splanchnicectomy (Smithwick), and total or subtotal thoracic sympathectomy (Grimson). All have a similar purpose. Each has its advantages and disadvantages. Peet (1935*B*), Freyberg and Peet (1937), Adson and Allen (1936), E. V. Allen and Adson (1938 and 1940), Craig (1939), Craig and Adson (1939), Crile (1937, 1938*A* and *B*, and 1939), and Peet, Woods, and Braden (1940) have made a number of reports of progress in recent years. Many surgeons have reported early experiences with these various techniques or modifications of them; the most significant articles are those by Smithwick (1944*A* and *B*, 1947, and 1948*B*), Hammarström (1947), Poppen and Lemmon (1947) de Takats *et al.* (1942), Ray (1945

and 1949), Hinton (1948), Heinbecker (1947), de Takats (1947, 1948, and 1949*A*), Fowler and de Takats (1949), Hammarström and Bechgaard (1950), and Linton *et al.* (1947).

To date, only two authors have published late results dealing with large numbers of cases: Peet and Isberg (1946) and Smithwick (1948*A*, 1949*A* and *B*). The results of Peet and Isberg will be considered in detail, and the latest statistics of Smithwick will form the basis for the discussion of the selection of patients for sympathectomy. Brief reference to the subdiaphragmatic technique and to total or subtotal thoracic and total sympathectomy will be made before discussing the results of the supradiaphragmatic (Peet) and the thoracolumbar (Smithwick) techniques.

A SUBDIAPHRAGMATIC SYMPATHETIC GANGLIONECTOMY AND SPLANCHNICECTOMY

This operation is performed in two stages spaced a week or two apart. The upper two lumbar ganglia are resected together with the greater, lesser, and least splanchnic nerves As a rule, it is possible to remove only 2 or 3 cm of these nerves, at most, and a portion of the celiac ganglion. There were no operative deaths in Allen and Adson's series of 224 cases (1940) The early results of this operation were reported by them and are summarized in Table XIX. Our experience with this operation, while not extensive, leads us to believe that regeneration, particularly of the great splanchnic nerves, may be a major factor in the large percentage of temporary and poor results which have been reported. Also, it is quite possible that failure to interrupt fibers which leave the great splanchnic nerves above the diaphragm and appear to run to the splanchnic bed along the aorta may be an additional factor influencing the outcome. One of us (R. H. S.) has had occasion to reoperate upon 5 patients at intervals of seven months to several years after subdiaphragmatic splanchnicectomy In all of these patients re-establishment of continuity of the great splanchnic nerve was found to have taken place on both sides.

B. SUBTOTAL OR TOTAL THORACIC SYMPATHECTOMY

Subtotal or total thoracic sympathectomies are indicated in certain cases where experience has shown that it is inadvisable to employ the thoracolumbar technique The latter appears to be contraindicated in patients who have palpitation associated with postural tachycardia. This tendency is clearly shown in the postural and cold blood-pressure tests by a rise in pulse rate of 30 beats per minute or more when the patient assumes

the upright position.* There are probably other forms of tachycardia in hypertensives which contraindicate thoracolumbar sympathectomy, especially in those individuals having palpitation associated with an abnormal accelerator response to exercise when tested by the Masters step

TABLE XIX

Results in 224 Patients Treated by Subdiaphragmatic Sympathetic Ganglionectomy and Splanchnicectomy for Hypertension Reported by Allen and Adson (1940)

(Patients followed postoperatively from three months to five years.)

EFFECT UPON BLOOD PRESSURE

Good	*Fair*	*Temporary or Poor*
27 (13%)	41 (18%)	156 (69%)

K.W.B. Group *	*Number of Cases*	*Good or Fair*	*Temporary or Poor*
1	11 (5%)	45%	55%
2	137 (61%)	33%	67%
3	69 (31%)	26%	74%
4	7 (3%)	0	100%

EFFECT UPON SYMPTOMS CORRELATED WITH FALL IN BLOOD PRESSURE

Effect upon Blood Pressure	*Headache*	*Dizziness*	*Tiredness*	*Thoracic Pain*	*Shortness of Breath*
Good or fair	94%	90%	58%	72%	65%
Temporary or poor	79%	92%	60%	59%	54%

* These cases are grouped according to the classification of Keith, Wagener, and Barker (1939) on the basis of eye-ground changes, described on p. 315.

test (a maximal accelerator response of 50 beats per minute or more). In patients with these forms of tachycardia, we have found that this abnormality may be intensified to a disabling degree following the thoracolumbar operation, and we have gradually reached the conclusion that under these circumstances an extensive transthoracic sympathectomy and splanchnicectomy is preferable. In these cases, for the past few years, we have removed the sympathetic trunks from T2 to T12 and splanchnic nerves in two stages about two weeks apart. This maneuver includes the cardioaccelerator fibers, since none appear to arise above the second thoracic level (Smithwick *et al.* 1949).

Another contraindication to thoracolumbar sympathectomy is coronary heart disease with angina pectoris, as this may be intensified unless the cardiac sympathetic outflow is included in the denervation. In such patients,

* The five successive pulse rates taken in the horizontal position and those in the upright position are averaged. If the difference is 30 or more, the response is regarded as abnormal.

and 1949), Hinton (1948), Heinbecker (1947), de Takats (1947, 1948, and 1949*A*), Fowler and de Takats (1949), Hammarström and Bechgaard (1950), and Linton *et al.* (1947).

To date, only two authors have published late results dealing with large numbers of cases: Peet and Isberg (1946) and Smithwick (1948*A*, 1949*A* and *B*). The results of Peet and Isberg will be considered in detail, and the latest statistics of Smithwick will form the basis for the discussion of the selection of patients for sympathectomy. Brief reference to the subdiaphragmatic technique and to total or subtotal thoracic and total sympathectomy will be made before discussing the results of the supradiaphragmatic (Peet) and the thoracolumbar (Smithwick) techniques.

A. SUBDIAPHRAGMATIC SYMPATHETIC GANGLIONECTOMY AND SPLANCHNICECTOMY

This operation is performed in two stages spaced a week or two apart. The upper two lumbar ganglia are resected together with the greater, lesser, and least splanchnic nerves. As a rule, it is possible to remove only 2 or 3 cm of these nerves, at most, and a portion of the celiac ganglion. There were no operative deaths in Allen and Adson's series of 224 cases (1940) The early results of this operation were reported by them and are summarized in Table XIX. Our experience with this operation, while not extensive, leads us to believe that regeneration, particularly of the great splanchnic nerves, may be a major factor in the large percentage of temporary and poor results which have been reported. Also, it is quite possible that failure to interrupt fibers which leave the great splanchnic nerves above the diaphragm and appear to run to the splanchnic bed along the aorta may be an additional factor influencing the outcome. One of us (R. H. S.) has had occasion to reoperate upon 5 patients at intervals of seven months to several years after subdiaphragmatic splanchnicectomy. In all of these patients re-establishment of continuity of the great splanchnic nerve was found to have taken place on both sides.

B. SUBTOTAL OR TOTAL THORACIC SYMPATHECTOMY

Subtotal or total thoracic sympathectomies are indicated in certain cases where experience has shown that it is inadvisable to employ the thoracolumbar technique. The latter appears to be contraindicated in patients who have palpitation associated with postural tachycardia. This tendency is clearly shown in the postural and cold blood-pressure tests by a rise in pulse rate of 30 beats per minute or more when the patient assumes

reason or another. The indications were excessive and disabling tachycardia, or the development of angina pectoris following thoracolumbar sympathectomy, or the failure of the latter to influence basal blood-pressure levels. As a result of this limited experience we have not been impressed with the advantages of total sympathectomy other than to correct tachycardia or relieve angina pectoris. The great majority of these complications could have been avoided had a subtotal or total thoracic sympathectomy been performed in the first place. Total sympathectomy, by inactivating both splanchnic vasoconstrictor and cardioaccelerator mechanisms, has resulted in prolonged and total disability in 4 of the 16 cases. After such an extensive denervation these patients have not been able to assume the upright position because of severe and persistent hypotension. This is well illustrated by Figure 59. Recent reports of experience with total sympathectomy have been published by Grimson, Orgain, *et al.* (1949) and Ray (1949).

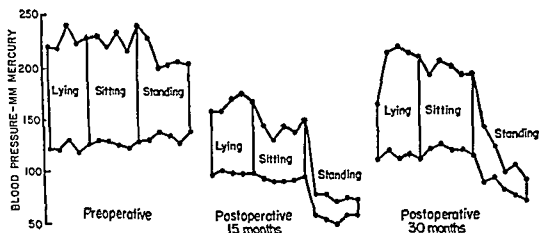


Fig. 59. Blood pressures in a totally sympathectomized patient.

Postural hypotension continues to persist to a disabling degree thirty months after operation. For over a year after operation, the patient was unable to stand for five minutes without fainting. Her activities are still greatly limited in spite of elastic stockings and a snug abdominal girdle. This has been an extremely trying experience for the patient, her family, and the doctors concerned. (Reproduced from Smithwick, R. H. "The surgical physiology of hypertension." *Surg Clin. North America*, 1949, 29: 1699–1730, courtesy of W. B. Saunders Co, Philadelphia.)

D. SUPRADIAPHRAGMATIC SYMPATHETIC GANGLIONECTOMY AND SPLANCHNICECTOMY

This operation is performed bilaterally in one stage. It was first described by the late Dr. Max Peet (1935*A*). An eleventh rib exposure of the extrapleural space is used. The great splanchnic nerves are removed from the celiac ganglia to the level of the seventh thoracic vertebra. Originally,

particularly when there is associated tachycardia on exertion, we feel that removal of the sympathetic trunks from the inferior cervical to the twelfth thoracic ganglia, inclusive, is the procedure of choice. A typical case in which both tachycardia and coronary heart disease with angina pectoris indicated the advisability of total thoracic sympathectomy and splanchnicectomy is illustrated by Figure 58. Subtotal or total thoracic sympathectomy is indicated in about 15 per cent of hypertensive patients who are to be treated surgically.

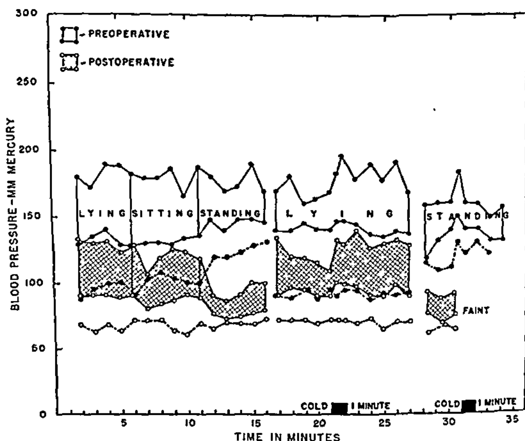


Fig. 58. Postural and cold blood-pressure tests and pulse rates compared before and sixteen days after total thoracic sympathectomy and splanchnicectomy.

This patient had angina pectoris and postural tachycardia before operation. In the acutely denervated state the blood-pressure levels were lower, there was moderately severe postural hypotension, and there was a slow pulse rate without postural acceleration. (Reproduced from Smithwick, R. H. "The surgical physiology of hypertension." *Surg. Clin North America*, 1949, 29: 1699–1730, courtesy of W. B. Saunders Co., Philadelphia.)

C. TOTAL SYMPATHECTOMY

Over the years one of us (R H. S.) has had occasion to extend thoracolumbar splanchnicectomy to total sympathectomy in 16 cases, for one

Table XXI. The effect of this operation upon blood-pressure levels in each of the six groups is shown in Table XXII. The status of the eye grounds, electrocardiograms, heart size, and renal function of the living cases in whom these data were available is summarized in Tables XXIII, XXIV, XXV, and XXVI, respectively.

TABLE XX

Preoperative Classification of 437 Cases of Hypertension Treated by Supradiaphragmatic Sympathectomy by Peet and Isberg (1946)

P. and I. Group	*Number*	*Per Cent*
1. Asymptomatic and early	5	1
2. Symptomatic, with no complicating disease	72	17
3. Organic heart disease	154	35
4. Cerebrovascular disease	53	12
5. Impaired renal function	41	9
6. Malignant hypertension	112	26
Total cases	437	

TABLE XXI

Subsequent Deaths in Table XX Cases According to Preoperative Classification of Hypertension

P. and I. Group	*Number*	*Per Cent of Total Deaths*	*Per Cent of Preoperative Group*
1	0	0	0
2	4	2	5
3	59	32	38
4	19	10	36
5	13	7	32
6	91	49	81
	186		

TABLE XXII

Analysis of the Effect of Surgical Treatment on Blood-pressure Levels Five to Eleven Years after Operation in 437 Patients (see Table XX) Including 186 Who Died

P. and I. Group	*Reduced to Normal, Per Cent*	*Definite Reduction, Per Cent*	*Significant Reduction, Per Cent*	*Unchanged, Increased, or Subsequent Death, Per Cent*
1	80	20	0	0
2	30	23 6	23 6	22 8
3	6	18	24	52
4	17	11.3	24 5	47.2
5	14 6	14 6	29.2	41.6
6	1.8	6.2	8	84

the lowest three thoracic ganglia were removed, but more recently the maneuver has been extended upward to include the eighth and at times the seventh ganglia (Peet, 1947). This operation appears to result in a more complete denervation of the splanchnic bed than the subdiaphragmatic technique. Nevertheless, it must be regarded as a partial denervation, since the visceral fibers from the first and second lumbar ganglia are not included. This operation also appears to safeguard against regeneration, particularly of the great splanchnic nerves, since a longer segment, 15 cm or more, is removed. Peet believed this to be an adequate operation for hypertension and was not convinced that more extensive procedures are necessary. This technique does not permit exploration of the adrenals and kidneys, which we feel should be a routine feature of every operation in hypertensive patients. Also, our experiences indicate that routine removal of the first and occasionally the second lumbar ganglia is important. There is, however, no question that supradiaphragmatic operation has been helpful in modifying the severity of hypertension and in slowing the progress of cardiovascular disease.

In a recent publication Peet and Isberg (1946) have discussed the results of this operation in a series of 437 cases operated upon five to twelve years previously. The patients were divided into six groups as follows: *

Group 1. Early, mild hypertension. These patients were entirely asymptomatic, had normal or Grade 1 fundi, and showed no evidence of cardiac, cerebral or renal involvement.

Group 2. Symptoms predominate. All patients in this group complained of symptoms and had abnormal fundi but displayed no evidences of cardiac, cerebral or renal impairment.

Group 3. Organic heart disease is predominant. In each case the diagnosis of heart disease was confirmed by either or both a definitely abnormal electrocardiogram and a teleoroentgenogram showing cardiac enlargement

Group 4 Cerebrovascular disease is predominant. Each patient in this group had one or more previous cerebral accidents.

Group 5. Impaired renal function is predominant. Each patient showed diminished concentrating ability and urea clearance values.

Group 6. Malignant hypertension. These patients had severe neuroretinitis with definite papilledema of 1 diopter or more and displayed a rapidly progressive, downhill course.

The number of cases in each P. and I. Group is shown in Table XX. Of these 437 cases, 251 (57.5 per cent) were alive five to eleven years after operation. The percentage of deaths in each of the six groups is shown in

* Peet, M. M., and Isberg, E. M. "The surgical treatment of arterial hypertension." *J. Amer. med. Ass.*, 1946, **130**: 467–473, courtesy of American Medical Association, Chicago.

TABLE XXVI

Effect of Surgical Treatment for Hypertension on Renal Concentrating *Ability of 117 Patients Living Five to Eleven Years after Operation* (see Table XX)

Preoperative Status	*Cases*	*Postoperative Result*		
		Significant Improvement	No Change	Worse
Normal function	62	0	51 (82.3%)	11 (17.7%)
Impaired function	55	20 (36.4%)	29 (52.6%)	6 (11%)
Total cases	117			

This constitutes one of the longest follow-up studies of the results of any form of treatment, surgical or otherwise. In contrast with available data on the prognosis following medical treatment, it would appear that the operation had been definitely worth while, particularly in the early stage of the disorder and in the cases having malignant hypertension. The operative mortality was reasonable, 3.6 per cent.

E. THORACOLUMBAR SYMPATHETIC GANGLIONECTOMY AND SPLANCHNICECTOMY

The thoracolumbar procedure appears to combine the advantages of both the subdiaphragmatic and supradiaphragmatic techniques and, if performed through a retropleural transdiaphragmatic retroperitoneal approach, does not increase the morbidity or mortality. This technique is indicated in about 85 per cent of hypertensive patients who are to be treated surgically. The transthoracic-transdiaphragmatic approach appears to be less desirable, since it may increase postoperative morbidity. The principal motive for the development of this transpleural exposure has been to increase the extent of the procedure in an upward direction with removal of the sympathetic trunks as high as the third or fourth thoracic ganglia. In our opinion it is most unlikely that this will prove worth while in the long run; in the great majority of cases removal of the sympathetic trunks bilaterally in two stages, from the eighth thoracic to the first lumbar ganglia, inclusive, together with the splanchnic nerves arising from this segment of the sympathetic trunk, is adequate. The operations are usually spaced ten days apart.

A more extensive removal of the lumbar chains results in a more marked postural hypotension and tachycardia postoperatively and greatly prolongs the period of convalescence. Removal of the second and third lumbar ganglia seems to be indicated only in patients who have an unusual degree

TABLE XXIII

Effect of Surgical Treatment for Hypertension on Eye Grounds of 146 Patients Living Five to Eleven Years after Operation (see Table XX)

Preoperative Status	*Cases*	*Postoperative Result*		
		Improved	No Change	Worse
Normal fundi	11	0	11 (100%)	0
Sclerosis only	30	2 (6.7%)	25 (83.3%)	3 (10%)
Angiospastic retinitis, with or without hemorrhages and exudates	88	72 (82%)	15 (17%)	1 (1%)
Papilledema	17	17 (100%)	0	0
Total cases	146			

TABLE XXIV

Effect of Surgical Treatment for Hypertension on the Electrocardiogram in 141 Living Patients Five to Eleven Years after Operation (see Table XX)

Preoperative Status	*Cases*	*Postoperative Status*		
		Significant Improvement	No significant Change	Worse
Normal electrocardiogram	84	0	78 (93%)	6 (7%)
Abnormal electrocardiogram	57	30 (52.7%)	24 (42%)	3 (5.3%)
Total cases	141			

TABLE XXV

Effects of Surgical Treatment for Hypertension on Heart Size, Measured by Teleoroentgenogram, of 128 Living Patients Five to Eleven Years after Operation (see Table XX)

Preoperative Status	*Cases*	*Postoperative Result*		
		Significant decrease in heart size	No significant change	Increase in heart-size
Normal heart size	80	0	73 (91 2%)	7 (8 8%)
Cardiac enlargement (18% or more above predicted normal area)	48	25 (52%)	21 (43 8%)	2 (4 2%)
Total cases	128			

blood-pressure levels, cardiovascular disease, and symptoms. In general, favorable changes in all of these respects have been noted in the majority of unselected cases in the early years after operation. More recently, data concerning the late effects of operation have become available and have been referred to in recent publications.

Because the early response to operation has been favorable in most unselected cases, it has seemed probable that surgical therapy would eventually prove to be worth while in many cases. In order to demonstrate the value of any form of treatment of hypertensive cardiovascular disease, it is necessary to show that the prognosis has been improved to a statistically significant degree. This is best accomplished by a comparison of mortality and survival rates for surgically and nonsurgically treated patients. One can gather a general impression of mortality rates for nonsurgically treated patients from representative reports in the literature. These are summarized in Table XXVII. It is apparent from a study of these data that the mortality

TABLE XXVII

Mortality among Hypertensive Patients Not Treated Surgically from Representative Published Reports

Author	*Number of Cases*	*Time Followed*	*Mortality*
Janeway (1913)	244	5–10 yr	81%
Blackford, Bowers, and Baker (1930)	202	5–11 yr	50%
Keith, Wagener, and Barker (1939)	219	5–9 yr	91%
H. Rasmussen and Boe (1945)	100	6 yr*	52%
Bechgaard (1946)	1038	4–11 yr	28%
Palmer, Loofbourow, and Doering (1948)	430	8 yr*	61%
Total	2233	Average	50%

* Average.

rates for different series of patients vary considerably—from 28 per cent to 91 per cent. Obviously, the patient material in the series studied must have differed widely. This is to be expected, since there are many variable factors which influence prognosis, particularly the severity of the changes in the cardiovascular system and the elevation of the resting diastolic blood-pressure level. To draw valid conclusions, therefore, patients must be divided into more comparable groups by taking these variable factors into consideration.

Keith, Wagener, and Barker (1939) were the first to recognize this fact and, in an outstanding publication, gave the prognosis for 219 medically treated hypertensive patients followed for five to nine years and divided into four groups on the basis of eye-ground changes:

of postural hypertension not associated with postural tachycardia. The portions of the sympathetic trunk removed in the various techniques which have been referred to are indicated diagrammatically in Figure 60.

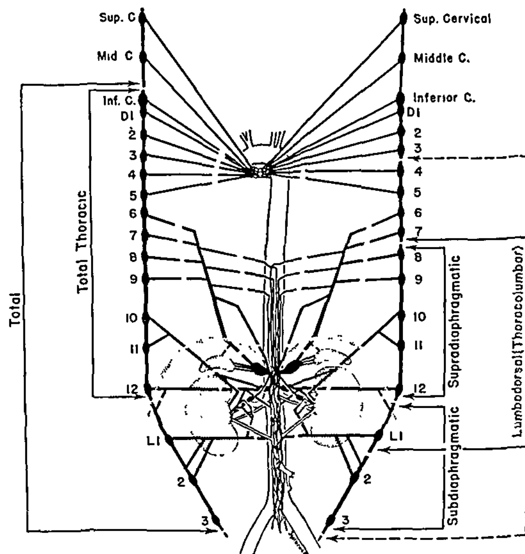


Fig. 60. Diagram to show extent of various sympathectomies for hypertension. Techniques for subdiaphragmatic and thoracolumbar sympathectomy and splanchnicectomy are illustrated on the right side, total thoracic and total sympathectomy on the left. All operations are, of course, performed bilaterally. (Reproduced from Smithwick, R. H. "The surgical physiology of hypertension." *Surg Clin. North America,* 1949, 29: 1699–1730, courtesy of W. B. Saunders Co, Philadelphia)

Since 1940 numerous reports dealing with the early results of this procedure have been published by one of us (R. H. S.) or his associates (Newell and Smithwick, 1947; P. D. White, 1946; Bridges *et al.*, 1946; Canabal *et al.*, 1945; Talbott *et al.*, 1943, and Smithwick, 1944*A*, and *B*, 1947, and 1948*B*). These have had to do with the effect of operation upon

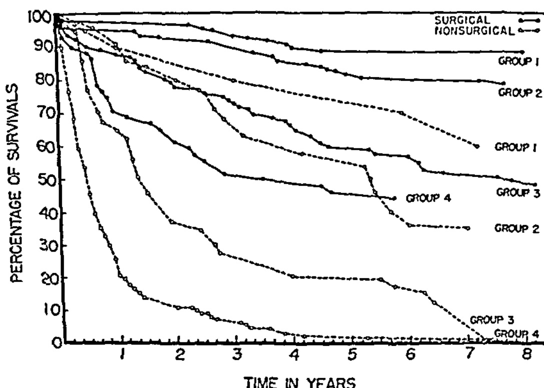


Fig. 61. Survival curves for surgically and nonsurgically treated hypertensive patients grouped according to Keith, Wagener, and Barker criteria.

The survival curves for our first 376 consecutive patients treated surgically are compared with Keith, Wagener, and Barker's 219 nonsurgically treated patients. Both series are divided into four groups, as explained in the text. The survival rates are higher in all groups in the surgical series The differences observed are statistically significant for K.W.B. Groups 2, 3, and 4. Both series were followed from five to nine years (see Table XXVIII).

IV. Selection of Cases for Sympathectomy

These comparisons indicate in a general way that surgery has significantly improved the outlook for hypertensive patients. They do not, however, clarify sufficiently the outlook for a specific patient. This is due to the fact that the patient material contained within each of the four groups referred to may vary tremendously because of variations in the status of the cerebral, cardiac, and renal areas among individuals having similar changes in the eye grounds. For this reason one of us (R. H. S.) has devised a plan for dividing hypertensive patients into four groups which takes intc consideration the changes in all vascular areas and in addition the age of the patient, the severity of the hypertension, and the response to sedation. We have not attempted to take the sex factor into consideration as yet because the difference in mortality rates for surgically treated patients, while slightly higher for males, is of no statistical significance. It is well known, how-

Patients in their Group 1, hereafter referred to as K.W.B. Group 1, had minimal evidence of spasm or sclerosis of the retinal arteries.

Those in K.W.B. Group 2 had sclerotic changes, particularly tortuosity, broadening of the light reflex, and arteriovenous compression.

Those in K.W.B. Group 3 had hemorrhages and/or exudate in addition to changes in the retinal arteries.

Those in K.W.B. Group 4 had measurable papilledema generally associated with hemorrhages and exudate and vascular changes of consequence. These are the patients with so-called "malignant hypertension."

The prognosis was found to vary according to the eye-ground changes. The mortality rates for their patients are given in Table XXVIII. Included

TABLE XXVIII

Mortality Rates for 219 Nonsurgically and 376 Surgically Treated Patients Grouped According to the Hypertension Criteria of Keith, Wagener, and Barker

	Nonsurgical Series (Keith, Wagener, and Barker)					*Surgical Series (Smithwick)*				
		At 5 years		From 5 to 9 years			At 5 years		From 5 to 9 years	
K W B Group	Number of cases	Number of deaths	Mortality	Number of deaths	Mortality	Number of cases	Number of deaths	Mortality	Number of deaths	Mortality
1	10	3	30%	4	40%	122	13	11%	14	12%
2	26	12	46%	17	65%	109	20	18%	23	21%
3	37	30	80%	34	92%	93	37	40%	48	52%
4	146	145	99%	145	99%	52	28	54%	29	56%
Total	219	190	87%	200	91%	376	98	26%	114	30%

are the mortality rates for the first 376 cases after thoracolumbar sympathectomy performed by Smithwick. The surgically treated cases have been followed for five to ten years and are also divided into four groups according to the eye-ground changes. It will be noted that the mortality rates are much lower in the surgical series There are not enough cases in K.W.B. Group 1 of the medical series to make possible a statistical comparison with the corresponding cases treated surgically. The difference in the mortality rates for K.W.B. Groups 2, 3, and 4 cases has great statistical significance in favor of the surgical group. These same data are presented in Figure 61 in the form of survival curves for both the Keith, Wagener, and Barker and the surgical series. The marked increase in the survival rates for the surgically treated patients is very apparent.

If a cerebral vascular accident has occurred, a neurologic consultation is requested, and such additional studies as skull plates, electroencephalograms, and lumbar puncture as seem indicated are carried out. It is also necessary to consider the possibility of a brain tumor simulating the picture of K.W.B. Group 4 hypertension. A cerebral neoplasm may develop in a hypertensive individual and, as has been shown by Palmer, Nyssens, and White (1948), it may be exceedingly difficult to recognize its coexistence. On numerous occasions this diagnosis has been missed during life and made only at post-mortem examination. Mistakes of this sort can only be avoided by careful neurological studies, which should include ventriculography in the more difficult cases.

A postural and cold blood-pressure test is performed as follows: The patient is required to have had at least forty-eight hours of bed rest except for lavatory privileges. The tests are carried out by technicians rather than physicians, since the former are generally able to obtain lower readings than a physician, presumably because the latter often acts as a pressor stimulus to the patient. Preliminary readings of blood pressure are taken on each arm. If no great discrepancy exists, the right arm is used. If there is a marked difference between the two sides, this is checked a number of times, and the arm with the higher reading is selected. The test is explained to the patient, and, after an additional rest period of fifteen to twenty minutes in the horizontal position, observations are begun. It is essential that the environment be quiet, comfortable, and pleasant All patients are transported to a special room for performance of the test, during which there should be no interruptions.

Readings of pulse and blood pressure are taken every minute for five minutes with the patient first lying, then sitting, then standing. The horizontal position is again assumed, and five further readings at one-minute intervals are taken, following which the opposite hand is immersed in ice water (4 to 5° C) up to the wrist for exactly one minute; readings are taken after thirty seconds and at the end of the sixty seconds of stimulation by cold. After this standard exposure to cold, readings are continued at one-minute intervals for an additional five minutes. The patient then assumes the upright position and after five preliminary readings at one-minute intervals the cold stimulus is repeated exactly as in the horizontal position. This is followed by five additional readings at one-minute intervals. The average of the first five readings in the horizontal position of the first portion of the postural and cold blood-pressure test is regarded as the resting blood-pressure level.

A sedative test is also performed in all cases. Following a light supper,

ever, that the mortality rates for nonsurgically treated patients is almost twice as high for males as for females. This makes the surgical results even more impressive for male patients, but does not alter the significance of the results in female patients. Eventually, when we are dealing with larger numbers, we shall divide the patients into two large groups and discuss the results for male and female patients separately.

An outline of the method of study used is given because the data serve as a basis for dividing cases into the four groups. If this information is available, it is then possible to judge with considerable accuracy the prognosis for a given patient In addition to a detailed history and physical examination, he should have his eye grounds examined with fully dilated pupils by an ophthalmologist. Occasional patients with continued hypertension have normal eye grounds. A simple classification has been used which divides the abnormal cases into four eye-ground grades (S. Eye Grades).

S. Eye Grade 1. In this grade are placed cases with only vascular spasm, generalized narrowing or irregular constrictions of any degree, without evidence of sclerosis, and without hemorrhage, exudate, or papilledema.

S. Eye Grade 2. Sclerotic changes, particularly arteriovenous compression, generally associated with tortuosity and increased light reflex, are placed in this group. Spasm might also be present, but hemorrhage, exudate, and papilledema are not in evidence.

S Eye Grade 3. This group includes patients with hemorrhage and/or exudate but without papilledema, regardless of the changes in the vessels

S. Eye Grade 4. Papilledema, measurable elevation of the disk, is the principal criterion for inclusion in this group. It is generally associated with hemorrhage and exudate and changes of consequence in the retinal arteries.

The cardiac status is determined by a cardiologist, whose clinical findings are supplemented by an electrocardiogram and a 7-ft heart plate with particular reference to the size and shape of the heart and the state of the aorta. The renal status is evaluated by urinalysis, a twelve-hour concentration test and an intravenous phenolsulfonephthalein test, the dye being injected after a period of forced fluid intake, and specimens collected at intervals of fifteen and thirty minutes and one and two hours. This ordinary test of renal function is useful in estimating the extent of renal damage in hypertensive patients and is the one we have come to rely upon most. A nonprotein nitrogen determination is made, and intravenous pyelograms are obtained routinely.

Blood studies include counts, smears, hemoglobin determinations, blood grouping, Rh factor, Hinton, blood sugar, serum protein, cholesterol, and chlorides The basal metabolic rate should be determined routinely.

TABLE XXX

Two Examples of Method for Determining Numerical Rating of Hypertensive Patients (Smithwick)

	Factors Considered		*Numerical Value*
Example 1:	Abnormal electrocardiogram		1
	Cerebrovascular accident without residual		1
	P.S.P. 20 per cent in 15 min		1
		Total	3 = Numerical rating
Example 2.	Abnormal electrocardiogram		1
	Enlarged heart		1
	P.S.P. 10 per cent in 15 min		3
		Total	5 = Numerical rating

A further subdivision of each of these classes into two smaller groups has been made on the basis of eye grounds, the severity of the changes in the cerebral, cardiac, and renal areas, and the resting diastolic blood-pressure level. This basis for subdividing the cases into our four S. Groups is indicated by Table XXXI. This method of classification controls many of the important variables and would seem to give greater assurance that the

TABLE XXXI

Classification of Hypertensive Patients: Criteria for Grouping (Smithwick)

S Group	*Numerical Rating*	*Other Factors*
1	Less than 4	Eye grounds S. Eye Grade O or 1 No changes in cerebral, cardiac, or renal areas
2	Less than 4	Eye grounds S. Eye Grade O or 1 with changes in cerebral, cardiac, and/or renal areas Eye grounds S. Eye Grade 2, 3, or 4 with or without changes in cerebral, cardiac, or renal areas
3	4 or more	Resting diastolic level below 140 mm Changes are present in cerebral, cardiac, and/or renal areas, but they do not include the following: *a.* C.V.A. with marked residual *b.* Frank congestive failure *c.* P.S.P. below 15 per cent in 15 min associated with a poor response to sedation
4	4 or more	Resting diastolic blood pressure below 140 mm [illegible] ...ined Pa[illegible] ...n or more

3 gr (180 mg) of sodium amytal are given by mouth at 6:00, 7:00, and 8:00 P.M. Hourly readings of pulse and blood pressure are recorded from 7:00 P.M. to 7:00 A.M. The lowest reading of systolic and diastolic blood pressure is taken as the response. This is evaluated by comparison with the horizontal or resting blood-pressure level as determined by the postural and cold test, and the diastolic response is regarded as the most significant figure. For patients with resting diastolic levels in the postural and cold test between 100 to 119 mm, the diastolic pressure during sedation should fall to 90 mm or less; for those in the range of 120 to 139 mm, it should fall to 100 mm or less; and for those with resting levels of 140 mm or more it should fall to 110 mm or less in order to be regarded as satisfactory. Better responses than this not infrequently occur and are regarded as good or excellent. A lesser response is not uncommon and is regarded as poor.

The plan which we use for dividing hypertensive patients into four groups *(S. Groups)* facilitates the discussion of the advisability of surgical treatment in a particular case. First of all, numerical values are assigned to each of numerous factors according to their importance in influencing prognosis. The factors and the corresponding numerical values are listed in Table XXIX. By adding the numerical values in each case, a number is arrived at which is called the numerical rating. Two examples of how to determine the numerical rating of a particular patient are given in Table XXX. The patients are divided into two large classes on the basis of the numerical rating. Those with numerical ratings of less than 4 are in the first, and those with ratings of 4 or more are in the second.

TABLE XXIX

Numerical Value of Various Factors Which Influence Prognosis in Hypertensive Patients (Smithwick)

Factors Considered	*Numerical Value of Each Factor*
Cerebrovascular accident without or with minor residual Abnormal electrocardiogram Enlarged heart Impending failure P S P. less than 25 per cent in 15 min or less than 60 per cent in 2 hr Age 50 or over Mild angina	1
[illegible]	2
P S P. less than 15 per cent in 15 min	3
Nitrogen retention	4

* Cerebral deterioration or hemiparesis.

diastolic levels of 110 mm or more may be operated upon. In spite of the statistical significance of the surgical results in the early years in S. Group 4 cases, we are not enthusiastic about recommending operation in these cases. The increased survival rate is of shorter duration, and the eventual mortality rate is very high. It would seem wiser to urge that patients be operated upon before they fall into this group. It is possible that combined medical and surgical therapy may offer S. Group 4 cases more than surgery alone, and we are studying this possibility at the present time. Also, one of us (R. H. S.) is studying the effect of subtotal adrenalectomy in conjunc-

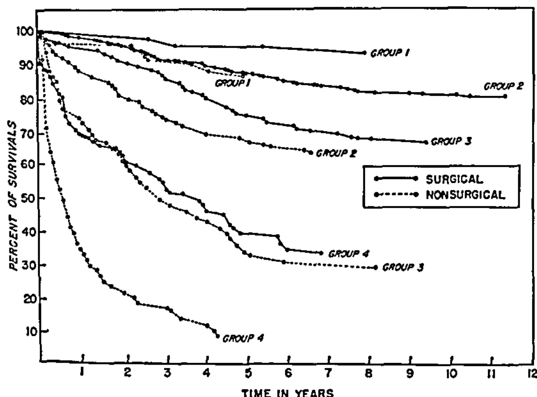


Fig. 62. Survival curves for surgically and nonsurgically treated hypertensive patients grouped according to Smithwick criteria.

Here, 596 surgically treated patients followed for four to twelve years are compared with 296 nonsurgically treated patients followed for four to ten years (see Table XXXII) Both series of patients are divided into four groups, as described in Table XXXI. There is, as yet, no statistically significant difference in the survival rates for S. Group 1 patients. The survival rate for surgically treated S. Group 2 patients is significantly increased over that for S. Group 2 nonsurgically treated patients. The survival rate for S. Group 3 surgically treated patients is greatly increased over that for S. Group 3 nonsurgically treated patients. The statistical significance of the difference in survival rates for these surgically and nonsurgically treated patients is very great. The survival rates for surgically treated S Group 4 patients is significantly increased over that for nonsurgically treated S. Group 4 patients for the first four years of observation. The significance is greatest in the early years and is becoming decreasingly significant with the passage of time. It is felt that surgery should be advised in S. Group 2 patients and urged in S. Group 3 patients. It may be employed in S Group 4 patients.

patient material in each S. Group is reasonably comparable. Consequently, comparisons between mortality and survival rates for surgically and nonsurgically treated patients in each group should have real value in deciding whether operation is advisable in a particular case.

The mortality rates for our nonsurgically and surgically treated patients are given in Table XXXII. The rates have been compared at four years

TABLE XXXII

Mortality Rates for 296 Nonsurgically and 596 Surgically Treated Hypertensive Patients Grouped According to Smithwick Criteria

	Nonsurgical Series (Smithwick)					*Surgical Series (Smithwick)*				
		At 4 years		From 4 to 10 years			At 4 years		From 4 to 12 years	
S Group	Number of cases	Number of deaths	Mortality	Number of deaths	Mortality	Number of cases	Number of deaths	Mortality	Number of deaths	Mortality
1	59	6	10%	8	14%	60	2	3%	4	7%
2	115	38	33%	42	37%	325	39	12%	70	22%
3	59	34	58%	42	71%	115	22	19%	39	34%
4	63	55	87%	57	90%	96	50	52%	63	65%
Total	296	133	45%	149	51%	596	113	19%	176	30%

There is no significant difference between the mortality rates for surgically treated patients in S Group 1 The mortality rate for surgically treated S. Group 2 and 3 patients is significantly lower than that of the nonsurgically treated cases, both for the first four years of observation and for the *entire period of observation* The same is true for surgically treated S. Group 4 patients for the first four years In S. Group 4 cases the difference between the mortality rates of the two series is greatest in the early years and is decreasing with the passage of time (see Fig. 66).

and at four to ten or twelve years for each group. There is no significant difference for S. Group 1 patients. The difference for S. Group 2 and 3 patients is statistically significant for each year and for the total period of observation in favor of the surgical series The statistical significance is becoming greater with each year of observation for both S. Groups 2 and 3. For S Group 4 cases, the difference in the mortality rates is most significant in the early years and is decreasing with the passage of time. These same data are presented in the form of survival curves in Figure 62. It is thus already apparent that operation has been worth while in cases falling into S. Groups 2 and 3. We recommend surgery for these patients. It will take a longer period of observation to decide whether surgery should be advised in S. Group 1 cases. We are reserving final decision in this matter for the present, but in the meantime we feel that S. Group 1 patients with severe symptoms which are difficult to manage medically and those with resting

surgical treatment (Palmer, 1947; Fishberg, 1948; and Evelyn *et al.*, 1949).

The operative mortality has been low following thoracolumbar operation, and it varies according to the cardiovascular status of the patients prior to operation. This is indicated by Table XXXIV, in which the operative mortality for the first 596 consecutive cases is given for each of the four S. Groups and for the entire series.

TABLE XXXIV

Operative Mortality of 596 Hypertensive Patients Grouped According to Smithwick Criteria

S. Group	*Number of Cases*	*Number of Deaths*	*Mortality*
1	60	0	0%
2	325	2	0.6%
3	115	3	2.6%
4	96	11	11.5%
Total	596	16	2.7%

V. Effect of Thoracolumbar Sympathetic Ganglionectomy and Splanchnicectomy upon Blood-pressure Levels, Cardiovascular Disease, and Symptoms

The effect of thoracolumbar sympathectomy and splanchnicectomy upon the blood pressure, cardiovascular system, and symptoms of the first 308 living patients to be followed for five to eleven years is summarized in Table XXXV. We have graded the effect of operation upon blood pressure as follows (S. Result Grades = Smithwick Result Grades):

S. Result Grade 1. Diastolic level reduced 20 mm or more and below 90 mm
S. Result Grade 2: Diastolic level reduced 20 mm or more and below 110 mm
S. Result Grade 3: Diastolic level reduced 10 to 19 mm and below 110 mm

TABLE XXXV

Status of Blood Pressure, Cardiovascular System, and Symptoms of 308 Surviving Surgically Treated Hypertensive Patients Five Years or More after Operation (Smithwick)

	Improved	*No Change*	*Worse*
Blood pressure	43%	44%	13%
Cardiovascular system *	60%	20%	20%
Symptoms	75%	18%	7%

* Cerebral, retinal, cardiac, and renal areas.

tion with sympathectomy and splanchnicectomy in certain S. Group 4 cases.

It should be noted that the selection of cases for sympathectomy is not based upon the effect of operation on blood-pressure levels but rather upon the effect on mortality and survival rates. We presume that lowering of blood pressure following surgery is a favorable physiological effect. At the same time, we know from experience that the mortality rate over a five- to eleven-year period of observation, while higher in patients having no lowering of blood pressure than in those with marked reductions, is nevertheless significantly lower in surgically treated than in control cases, *regardless of the effect upon blood-pressure levels.* Surgery for patients falling into S. Groups 2 and 3 can therefore be considered worth while, even if it results in an insignificant reduction in pressure, or none. This is supported by the facts presented in Table XXXIII, in which the mortality rates for sur-

TABLE XXXIII

Mortality Rates for Surgically Treated Hypertensive Patients According to Effect upon Blood-pressure Levels

	Surgical Cases (Smithwick)				*Nonsurgical Control Cases (Smithwick)*	
	B P reduced		B P. not reduced			
S Group	*Number of cases*	*Mortality*	*Number of cases*	*Mortality*	*Number of cases*	*Mortality*
1	42	2%	30	10%	41	10%
2	151	7%	129	14%	70	27%
3	27	7%	56	30%	31	65%
4	7	14%	24	79%	19	69%

The effect of operation on blood pressure was determined at the end of one year. The mortality rates for the surgical cases were then calculated for a five- to eleven-year period

whether the blood pressure is reduced or not, over that for the control series. The mortality rate for surgically treated patients, both with and without significant reductions of blood pressure, is significantly lower than for the control cases in both S. Groups 2 and 3. The mortality rate for S Group 4 cases treated surgically, who had significantly reduced blood pressure, is very much lower than for the control series, while there is no significant difference in the mortality rate for surgically treated patients in S Group 4 who did not have a significant reduction in blood pressure over that noted in the control series

gically treated patients having significant reductions in blood-pressure levels and those with insignificant or no reductions are compared with those from our nonsurgically treated control series It seems important to emphasize this point, because certain authors seem to have put too much stress on reduction in blood-pressure levels as a measure of success or failure of

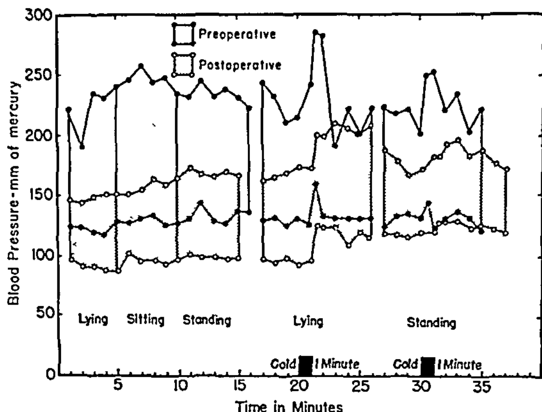


Fig. 63. Blood pressures before and eighty-seven months after operation in a forty-two-year-old female (Patient A.).

This patient was known to have had hypertension six years before operation. Eye grounds were S. Eye Grade 3, brain normal, electrocardiogram abnormal, heart abnormal in size and shape with congestive failure, aorta tortuous. There was albuminuria and P.S.P. output was reduced to 20 per cent in fifteen minutes, 45 per cent in two hours. On sedation, the blood pressure fell to 146/92. Blood-pressure levels before and at various intervals after operation are given below. Preoperative levels were determined after a period of forty-eight hours' rest, postoperative data were secured after a fifteen-minute rest in a horizontal position. According to these data, the patient was classified in S. Group 3 (numerical rating 4, see Table XXXI). The kidney biopsy showed the patient to have had chronic vascular nephritis Grade 1, with microscopical changes such as are illustrated by Figure 71. Eighty-seven months after operation the eye-ground changes were S. Eye Grade 2, electrocardiogram abnormal, the heart abnormal in size and shape but normal in function, the aorta elongated and tortuous. There was albuminuria and P.S.P. output was 20 per cent in fifteen minutes. There has been marked symptomatic improvement, and this is an S. Result Grade 1 blood-pressure result.

Blood-pressure Data

Time Observation	Conditions	Lying	Standing	Ceiling Cold Lying	Ceiling Cold Standing	Cold Response Lying	Cold Response Standing
Preoperative:	Resting	227/123	230/133	284/158	250/144	+44/+34	+50/+14
Postoperative:							
12 mo	Ambulatory	141/89	146/107	130/110	138/106	+14/+26	−34/−10
24 mo	Ambulatory	106/66	90/68	140/90	108/82	+32/+22	−8/−2
36 mo	Ambulatory	143/90	156/110	180/96	158/120	+18/+10	+24/+18
45 mo	Ambulatory	150/91	159/111	178/106	160/124	+38/+16	+2/+16
60 mo	Ambulatory	165/95	151/114	190/118	174/120	+36/+28	+10/+6
87 mo	Ambulatory	146/89	166/98	200/124	182/118	+28/+20	+10/+10

The comparisons are made between the levels in the horizontal position. S. Result Grade 1 and 2 reductions are equally marked, and S. Result Grade 3 is slight. Cases in S. Result Grades 1, 2, or 3 are regarded as having had a significant reduction in blood pressure (Figs. 63, 64, and 65). In the remaining cases the blood pressure was not significantly reduced (Figs. 66 and 67).

It should be appreciated that it is difficult, even impossible, to draw an exact line of demarcation between what constitutes a significant and an insignificant change in blood-pressure level after operation. The criteria which have been used seem reasonable, but the study of blood pressure in hypertensive patients is inaccurate at best. It is quite possible that at times, particularly when patients are asleep, the blood-pressure levels of many of them who do not seem to have significant reductions when ambulatory are actually much lower than before operation. Also, many patients who have no change in diastolic levels may have a definite reduction in systolic levels with a narrowing of the pulse pressure. This is well illustrated by Figure 66, in which the levels before and four years after operation are compared, and the difference is classified as not significant. The change well may be significant. In any case, the difference in pressure is less significant than in the cases classified as having reduced levels. It should be remembered that the method of study used compared ambulatory postoperative levels with resting preoperative levels—an obvious but unavoidable source of error. This tends to an underestimation of the frequency with which blood-pressure levels may have been affected. Since the beneficial effects of operation are not solely dependent upon a so-called "significant" reduction in the level, discussions of changes in blood pressure are more of academic than of practical importance. It is of interest that in over 40 per cent of living patients and about 25 per cent of the gross series, prolonged and significant reduction of blood pressure for five years or more has followed thoracolumbar sympathectomy. This indicates the importance of the neurogenic factor in hypertensive cardiovascular disease. Since comparable reductions have been noted in over 60 per cent of patients in the early years after operation, it is apparent that the neurogenic factor is of importance in increasing peripheral resistance in at least two thirds of all patients.

The cases we have concerned ourselves with primarily are those with persistent hypertension with demonstrable cardiovascular disease. It may be that in the stage of intermittent hypertension, when cardiovascular disease is rarely demonstrable, surgery will be even more effective. Data are being accumulated upon this point and will be published subsequently by one of us (R. H. S.). It is possible, even probable, that less radical surgery,

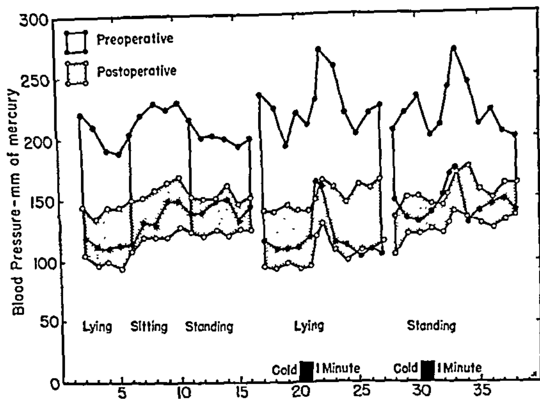


Fig. 65. Blood pressures before and sixty months after operation in a thirty-two-year-old male (Patient C).

This patient was known to have had a cerebrovascular accident without residual prior to operation. Eye-ground changes were S. Eye Grade 1, electrocardiogram abnormal, heart normal in size but abnormal in shape, and aorta tortuous. There was a trace of albuminuria, and P.S.P. output was 15 per cent in fifteen minutes, 45 per cent in two hours. On sedation, the blood pressure fell to 120/90. Blood-pressure levels before and at intervals after operation are given below. Preoperative levels were determined after a period of forty-eight hours' rest; postoperative data were secured after a period of fifteen minutes' rest in a horizontal position According to these data, the patient was classified in S. Group 3 (numerical rating 4; see Table XXXI) Sixty months after operation the studies of the cardiovascular system revealed no recurrence of cerebrovascular accident. The eye grounds were normal, electrocardiogram was slightly abnormal, heart was normal in size and abnormal in shape, and the aorta was tortuous and widened. There was a slight trace of albuminuria, P.S P. output was 10 per cent in fifteen minutes. There has been marked symptomatic improvement. This is an S. Result Grade 3 blood-pressure result. The renal biopsy showed grade 3 changes, as illustrated by Figure 73.

Blood-pressure Data

Time				*Ceiling Cold*		*Cold Response*	
Observation	*Conditions*	*Lying*	*Standing*	*Lying*	*Standing*	*Lying*	*Standing*
Preoperative	Resting	196/114	198/144	268/174	272/174	+58/+54	+62/+20
Postoperative							
12 mo	Ambulatory	156/109	160/122	210/138	184/142	+58/+42	+28/+8
60 mo	Ambulatory	144/100	153/124	174/130	172/140	+32/+34	+26/+16

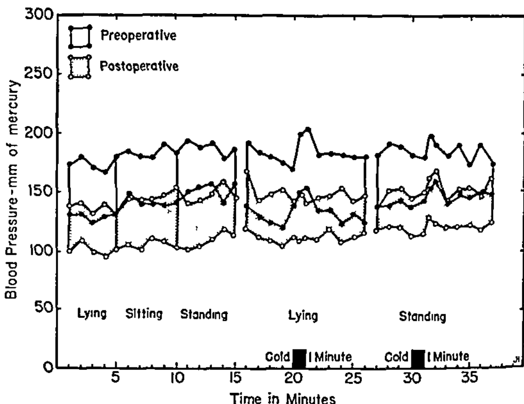


Fig. 64. Blood pressures before and seventy-seven months after operation in a thirty-seven-year-old male (Patient B).

This patient was first informed of his hypertension during an examination to determine the cause of shortness of breath. Eye-ground changes were S. Eye Grade 4, brain not affected, heart normal in size and shape, and aorta normal. The electrocardiogram was slightly abnormal and indicated some coronary heart disease. There was no albuminuria, and P.S.P output was 25 per cent in fifteen minutes and 47 per cent in two hours On sedation, the blood pressure fell to 130/90. Blood-pressure levels before and at various intervals after operation are given below Preoperative levels were determined after a period of forty-eight hours' rest; postoperative data were secured after a fifteen-minute rest period in a horizontal position The kidney biopsy showed the patient to have chronic vascular nephritis, Grade 4 (see Fig 74). According to these data, the patient was classified in S. Group 2 (numerical rating 2; see Table XXXI). Seventy-seven months after operation the eye-ground changes were S. Eye Grade 1, the heart was normal in size and shape, and the electrocardiogram was also normal. There was no albuminuria, and P.S P. output had risen to 45 per cent in fifteen minutes There has been marked symptomatic improvement This is an S. Result Grade 2 blood-pressure result.

Blood-pressure Data

Time Observation	*Conditions*	*Lying*	*Standing*	*Ceiling Cold Lying*	*Ceiling Cold Standing*	*Cold Response Lying*	*Cold Response Standing*
Preoperative:	Resting	175/128	189/152	204/154	198/160	+38/+18	+18/+18
Postoperative:							
12 mo	Ambulatory	127/90	132/105	124/104	150/118	−10/+10	+12/+10
26 mo	Ambulatory	106/68	109/77	90/60	120/80	+2/+0	+4/+2
41 mo	Ambulatory	113/80	128/94	110/90	124/94	+0/+12	+4/+6
60 mo	Ambulatory	117/87	128/102	130/102	144/116	+18/+14	+20/+10
77 mo	Ambulatory	133/100	147/109	150/112	168/108	+8/+0	+16/+12

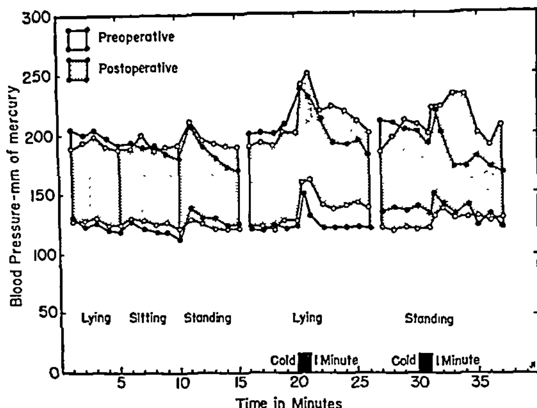


Fig. 67. Blood pressures before and ninety-five months after operation in a thirty-eight-year-old female (Patient E).

Hypertension was first discovered during her second pregnancy. Eye-ground changes were S. Eye Grade 4, brain was normal, electrocardiogram was abnormal, heart was normal in size and function. There was a slight trace of albuminuria and there was a P.S P. output of 20 per cent in fifteen minutes, 40 per cent in two hours On sedation, the blood pressure fell to 110/70 Blood-pressure levels before and at various intervals after operation are given below. Preoperative levels were determined after a period of forty-eight hours' rest; postoperative data were secured after a fifteen-minute rest in a horizontal position. According to these data, the patient was classified in S. Group 2 (numerical rating 2, see Table XXXI). The kidney biopsy showed the patient to have chronic vascular nephritis Grade 1, with changes such as are illustrated in Figure 71. Ninety-five months after operation the eye-ground changes were S. Eye Grade 1, electrocardiogram was slightly abnormal, the heart was normal in size and shape. There was no albuminuria, and P.S.P. output was 25 per cent in fifteen minutes. There has been marked symptomatic improvement. The electrocardiographic changes are illustrated in Figure 68. There is no significant difference in the levels, although at times during the follow-up period they were found to be lower.

Blood-pressure Data

Time				*Ceiling Cold*		*Cold Response*	
Observation	*Conditions*	*Lying*	*Standing*	*Lying*	*Standing*	*Lying*	*Standing*
Preoperative:	Resting	197/127	181/128	240/150	220/150	+40/+26	+26/+18
Postoperative:							
20 mo	Ambulatory	172/106	159/119	216/140	212/144	+38/+52	+44/+34
36 mo	Ambulatory	135/106	161/126	194/140	184/138	+60/+40	+30/+30
63 mo	Ambulatory	186/117	166/123	220/148	224/150	+30/+38	+50/+30
86 mo	Ambulatory	166/98	165/115	222/146	230/150	+46/+48	+70/+46
95 mo	Ambulatory	193/126	195/123	248/160	220/136	+48/+34	+22/+16

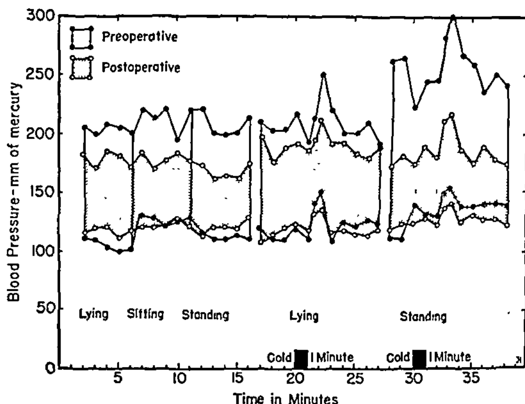


Fig. 66. Blood pressures before and forty-eight months after operation in a forty-eight-year-old male (Patient D).

This patient was found to have S. Eye Grade 4 eye-ground changes and an abnormal electrocardiogram. The heart was abnormal in size and shape and showed early signs of congestive heart failure, the aorta was normal. There was some albuminuria, there was a P.S P. output of 25 per cent in fifteen minutes and 70 per cent in two hours. On sedation, his blood pressure fell to 150/100. The blood pressures before and at intervals after operation are given below. Preoperative levels were determined after a period of 48 hours' rest; postoperative data were secured after a fifteen-minute rest period in a horizontal position. According to these data, the patient was classified in S. Group 3 (numerical rating 5, see Table XXXI). The kidney biopsy showed the patient to have chronic vascular nephritis Grade 3 changes, such as are illustrated by Figure 73. Forty-eight months following the operation the eye-ground changes were S. Eye Grade 2, electrocardiogram was normal, heart was normal in size and shape, and the aorta was elongated and tortuous P.S P. output was 38 per cent in fifteen minutes There was a slight trace of albuminuria. The electrocardiogram and heart changes are illustrated in Figures 69 and 70. There has been marked symptomatic improvement. The change in blood-pressure levels has *not been classified as significant, although it well may be.*

Blood-pressure Data

Time Observation	*Conditions*	*Lying*	*Standing*	*Ceiling Cold* *Lying*	*Standing*	*Cold Response* *Lying*	*Standing*
Preoperative:	Resting	204/104	206/112	248/150	298/154	+54/+40	+52/+26
Postoperative:							
15 mo	Ambulatory	145/94	125/103	198/126	164/120	+26/+16	+12/+2
48 mo	Ambulatory	177/116	167/120	212/136	216/140	+26/+20	+36/+18

ing quotation from the article of Canabal *et al.* (1945) is pertinent.* "Having *become interested in these electrocardiographic changes following splanchnic* sympathectomy, we sought in vain for published reports of comparable and adequate control studies, that is, studies of the evolution of the hypertensive

TABLE XXXVI

Electrocardiograms of Nonsurgically and Surgically Treated Hypertensive Patients Followed for Five Years or More

Author	*Treatment*	*Number of Cases*	*Improved*	*No Change*	*Worse*
Canabal, Warneford-Thomson, and White, P. D. (1945)	Nonsurgical	50	10%	40%	50%
Rasmussen and Boe (1945)	Nonsurgical	39	8%	56%	36%
Isberg and Peet (1948)	Surgical	184	19%	76%	5%
Smithwick	Surgical	181	31%	55%	14%

electrocardiogram in patients without such operation. Hence, we have collected as many such data as we have as yet been able to find which were based upon adequate criteria. This search has been difficult and has yielded only fifty cases." Examples of the course of electrocardiograms following thoracolumbar sympathectomy with reduction in heart size are illustrated by Figures 68, 69, and 70. Favorable changes in eye grounds, heart size, and renal function have also been reported by Peet and Isberg (1946 and 1948), by Isberg and Peet (1948), and by Smithwick (1948*A*, 1949*A* and *B*) in patients followed for five years or more. Typical biopsy specimens showing renal vascular disease graded 1 to 4 are illustrated by Figures 71, 72, 73, and 74. Since there are no comparable data in the literature for nonsurgically treated patients, it is useless to discuss this aspect of the matter in detail at this time. In addition to favorable changes in these areas, lack of progression was also noted in many cases, with progression of cardiovascular disease in 20 per cent at most, as indicated by Table XXXV. Symptomatic improvement was obtained by 75 per cent of patients followed for five years or more.

There seems to be little correlation between relief of symptoms and changes in blood-pressure levels. The symptom which is most consistently relieved or improved is headache, particularly the occipital variety, which is present in the early morning hours and tends to wear off during the day. In asking patients to evaluate their symptoms after operation, we have re-

* Canabal, E. J., Warneford-Thomson, H. F., and White, P. D. "The electrocardiogram in hypertension. III. Electrocardiograms of hypertensive patients followed for a long time without splanchnic resection in comparison with those in patients who had had splanchnic resection." *Amer. Heart J.*, 1945, 30: 189–194, courtesy of C. V. Mosby Co., St. Louis.

such as supradiaphragmatic sympathectomy and splanchnicectomy undertaken at an earlier stage of the disorder, would prevent the development of the full-blown picture of hypertensive cardiovascular disease and give young and middle-aged individuals a more nearly normal life expectancy. The degree of success which has resulted from more radical procedures, instituted at a stage in the disease which may eventually be regarded as not the optimal time for interference, justifies a careful investigation of surgical therapy at an earlier stage.

As indicated by Table XXXV, the status of the cardiovascular systems of patients who have been re-examined five years or more after operation is improved in 60 per cent, unchanged in 20 per cent, and worse in 20 per cent. In other words, 80 per cent of the patients show no significant deterioration. As concerns this aspect of the problem, the preoperative changes in the cerebral, cardiac, and renal areas were graded as is shown in Table XXIX. In addition, the eye grounds were graded from 0 to 4, a corresponding numerical value being assigned to each grade. The changes in the cerebral, retinal, cardiac, and renal areas were graded before and five years or more after operation, and the totals were compared. If, for instance, the total was 8 before and 4 after, the over-all status of the cardiovascular system was considered improved. In occasional cases the over-all picture is improved, although there may be slight progression of disease in one area with favorable changes in other areas which counterbalance it. In the great majority of cases showing over-all improvement, there is no evidence of progression of disease in any area. In cases showing over-all deterioration the evidence of progression is usually minor in nature. The impressive part of this study is the lack of evidence of deterioration of the cardiovascular system over long periods of observation. This is in keeping with the significantly reduced mortality rates, for over 90 per cent of patients with hypertensive cardiovascular disease die of some vascular complication—cardiac, cerebral, or renal, in that order.

In evaluating therapy the rate of progression of cardiovascular disease will be an important yardstick. To date, almost no evidence of this sort is available for nonsurgically treated patients. All that can be referred to at this time are the changes in the electrocardiograms of nonsurgically treated patients followed for five years or more. The findings of Canabal *et al.* (1945) and of H. Rasmussen and Boe (1945) are compared with those of Isberg and Peet (1948) and with those of Smithwick in Table XXXVI. Again, the difference between surgically and nonsurgically treated patients is statistically in favor of the surgical series. In this connection the follow-

ing quotation from the article of Canabal *et al.* (1945) is pertinent.* "Having become interested in these electrocardiographic changes following splanchnic sympathectomy, we sought in vain for published reports of comparable and adequate control studies, that is, studies of the evolution of the hypertensive

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quested them to balance all of the untoward effects of operation, including postoperative discomfort and the period of convalescence, against the benefit they have derived. The figure of 75 per cent was arrived at in this manner. In addition, 18 per cent of cases felt there had been no significant

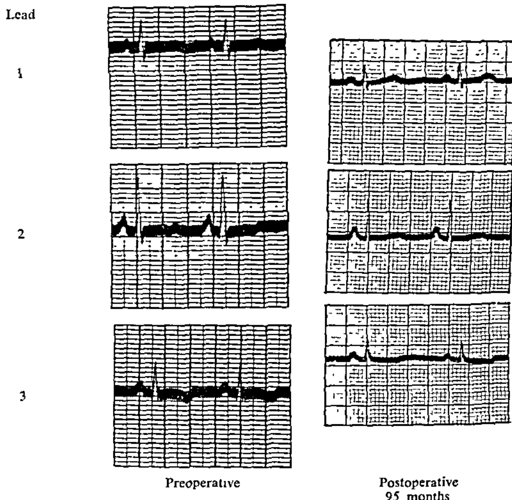


Fig. 68. Electrocardiogram before and ninety-five months after thoracolumbar sympathectomy and splanchnicectomy (Patient E).

Before operation the T wave in lead 1 was low and inverted in leads 2 and 3 Ninety-five months following operation the T waves were low but upright in leads 1 and 2. The standard leads have returned to normal (see Fig 67).

change one way or the other Many of these patients had few symptoms originally. Only 7 per cent felt that their symptoms were worse five years or more after operation. From every viewpoint the status of our living hypertensive patients evaluated five years or more after operation is very gratifying. There has been improvement or lack of progressive increase of blood pressure, of cardiovascular disease, and of symptoms in 80 per cent of the survivors.

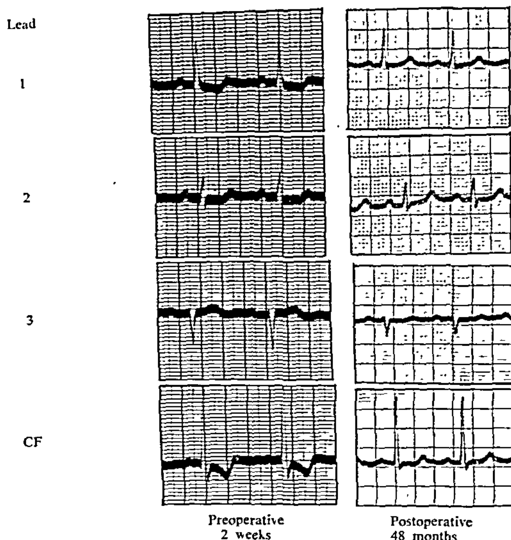


Fig. 69. Electrocardiogram before and forty-eight months after operation (Patient D).

Preoperative electrocardiogram showed left axis deviation and inverted T waves in the first standard lead and fifth chest lead, accompanied by depressed S-T segments. These changes were interpreted as being consistent with myocardial disease and digitalis effect. Forty-eight months following operation, T waves in the electrocardiogram are within normal range. The patient has not taken digitalis since the immediate postoperative period (see Figs. 66 and 70).

VI. Pregnancy following Thoracolumbar Sympathetic Ganglionectomy and Splanchnicectomy

An increasing number of patients are being permitted to attempt pregnancy following a favorable response to extensive sympathectomy. The course of pregnancy in 14 patients was recently discussed by Newell and Smithwick (1947). These patients had continued hypertension with varying degrees of cardiovascular damage prior to sympathectomy. Approxi-

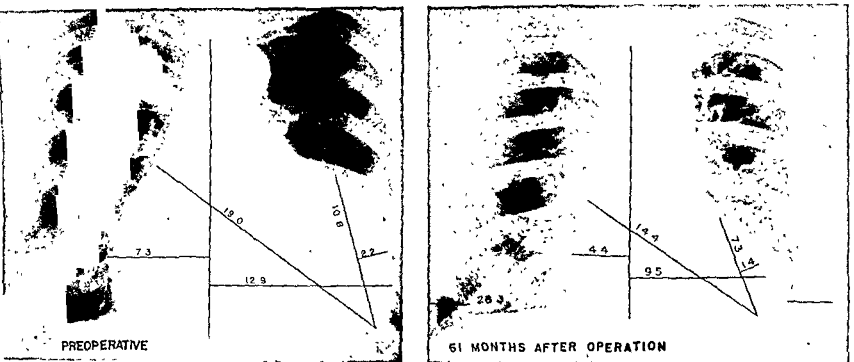


Fig. 70. Pre- and postoperative cardiac measurements (Patient D).

Preoperative: Right median 7.3 cm, left median *12.9 cm*, transverse diameter 19.0 cm, pulmonary field *29.0* cm, *length* 20.2 cm, length of left ventricle 10.8 cm, thickness of left ventricle 2.2 cm. The heart is abnormal in size and shape. The lung fields are clear.

Sixty-one months after operation: Right median 4.4 cm, left median 9.5 cm, transverse diameter 14.4 cm, pulmonary field 29.3 cm, length of left *ventricle* 7.3 cm, thickness of left ventricle 1.4 cm. The heart *is within* normal limits of size and contour (see Figs. 66 and 69).

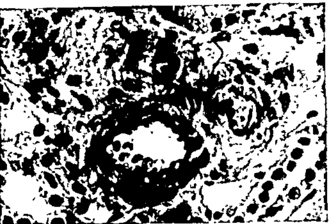
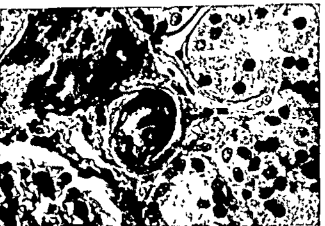





Fig. 71. *(Top, left)* Chronic vascular nephritis, Grade 1 (Patient A) (see Fig. 63).
Fig. 72. *(Top, right)* Chronic vascular nephritis, Grade 2.
Fig. 73. *(Bottom, left)* Chronic vascular nephritis, Grade 3 (Patient C) (see Fig. 65).
Fig. 74. *(Bottom, right)* Chronic vascular nephritis, Grade 4 (Patient B) (see Fig. 64).

mately half of the patients had chronic pyelonephritis. Three patients had malignant hypertension. The time elapsing between operation and pregnancy averaged thirty months, with the exception of one woman on whom sympathectomy was performed during the first trimester. Admission blood-pressure levels prior to sympathectomy averaged 196/130, prior to pregnancy 135/87, two weeks post partum 134/89, and six or more weeks post partum 133/87. All but one patient obtained living children and did not appear to have suffered cardiovascular damage. One stillbirth resulted from premature separation of the placenta. This patient subsequently obtained a living child at a second pregnancy. In 9 women the pregnancy was entirely uneventful, without elevation of blood pressure or signs of toxemia. In 5, signs of toxemia with elevation of blood pressure varying from slight to marked necessitated termination of the pregnancy. All obtained living children, as this complication occurred late in pregnancy. The series has increased considerably. Two additional patients having severe continued hypertension were operated upon in the first trimester and delivered uneventfully at term. Several other patients, one with large bilateral polycystic kidneys, have become pregnant at various intervals after operation and all have had an uneventful course and obtained living babies. It is our impression that, *following a satisfactory response to operation, pregnancy,* if carefully supervised, appears to be safe and permissible. These experiences lead us to believe that following this operation certain hypertensive women may be able to tolerate pregnancy which would otherwise be impossible or extremely hazardous. This is particularly true in the younger age group with severe essential and even malignant hypertension, with or without chronic pyelonephritis.

VII. Other Surgical Measures in the Treatment of Hypertensive Cardiovascular Disease

A. REMOVAL OF PHEOCHROMOCYTOMAS

Hypertension due to a pheochromocytoma is rare. Since removal of such a tumor is almost always successful, it is important that this diagnosis be kept in mind as a possibility in every hypertensive patient. To date there are about 250 case reports in the literature. Only about one third of the patients were operated upon. The tumors in the other cases were discovered at autopsy.

Most of these patients have a history of paroxysmal attacks of hypertension associated most commonly with headache, palpitation, vomiting, and sweating. It is important to realize, however, that some patients do not have

these attacks and may be regarded as having so-called "essential" hypertension. In such cases, unexplained temperature elevations, excessive sweating, a basal metabolic rate of +20 or more, elevated blood sugar, and rapid heartbeat, particularly postural tachycardia associated with postural hypotension, should lead one to suspect the presence of a pheochromocytoma.

The introduction of adrenergic blocking drugs by Goldenberg *et al.* (1947) has helped to confirm the presence of a pheochromocytoma and is a much safer procedure than the precipitation of an attack with histamine or Mecholyl. The use of the latter drugs is questionable in patients with high sustained types of hypertension. An adrenergic blocking drug should be available to stop the attack if precipitated in such cases.

These tumors are small, as a rule about 4 cm in diameter. They are occasionally demonstrated by pyelography. Perirenal air injections can be made but are not without serious hazard. The vast majority of the tumors arise in the adrenal gland and are unilateral. Bilateral tumors are rare. Occasionally, they arise from ganglionic tissue in the lumbar region and very rarely in the thorax. So far, two cases are on record in which the tumors were intracranial in position.

It is well to explore the adrenal glands during the performance of a thoracolumbar sympathectomy. In this way, tumors will not be overlooked. The thoracolumbar approach with division of the diaphragm is the best exposure for removing a tumor when it is known to be present. In operations on patients with essential hypertension by an approach which does not permit exploration of the adrenal glands, unusual precautions should be taken to exclude the presence of a pheochromocytoma by appropriate preliminary studies. The signs, symptoms, and procedures which are helpful in making the diagnosis of pheochromocytoma have recently been discussed by Smithwick *et al.* (1950).

B. UNILATERAL NEPHRECTOMY

Brief mention should be made of unilateral nephrectomy in the treatment of hypertensive cardiovascular disease. Following the brilliant animal experiments of Goldblatt *et al.* (see p. 299) the possibility that a diseased kidney might elaborate a pressor substance and cause hypertension received widespread consideration. As a result a considerable number of patients were treated by nephrectomy. A recent review of reported results by Homer Smith (1948) reveals a number of cases in which the hypertension has been favorably modified without doubt. So far, it has been impossible to predict which patients will respond. It is generally agreed that the indications for nephrectomy in hypertensive patients should be the same

as for nonhypertensive individuals. Only seriously damaged or nonfunctioning kidneys should be removed. The opposite kidney should be normal. It is inadvisable to remove the poorer of two involved kidneys. Since there are inadequate data concerning the late results of unilateral nephrectomy, and since the chances for improvement for a short time are slight (20 per cent, according to Smith, 1948), it seems best to recommend that unilateral thoracolumbar sympathectomy and splanchnicectomy be performed at the time of nephrectomy.

C. ADRENALECTOMY

Partial adrenalectomy was one of the first procedures to be tried in the surgical approach to hypertensive cardiovascular disease. A portion of both adrenal glands was removed with and without associated sympathectomy and splanchnicectomy. The results were not impressive. This may have been due to the removal of an inadequate amount of adrenal tissue. It is known that hypertension cannot exist in the absence of the adrenal cortex. The advent of replacement therapy has made possible a further trial of subtotal and even total adrenalectomy, alone or in combination with sympathectomy and splanchnicectomy. At present, there are no data of importance concerning this re-evaluation of adrenalectomy. One of us (R. H. S.) is exploring this matter in certain S. Group 4 cases (Table XXXI). It does not seem proper at this time to use this procedure in S. Group 1, 2, or 3 cases, since the prognosis for these patients is so satisfactory following sympathectomy and splanchnicectomy alone (Fig. 62). Subtotal or total adrenalectomy must be regarded as highly experimental at the present time.

VIII. Comments on the Surgical Treatment of Hypertension Based on Massachusetts General Hospital Study, 1945 to 1950

During the first decade of these studies all the operations on hypertensives which have been reported above were done at the Massachusetts General Hospital. In 1945 Dr. Smithwick left to assume his duties as Professor of Surgery and Head of the Department of Surgery of the Boston University School of Medicine and the Massachusetts Memorial Hospitals. In order to continue the study of hypertension at the Massachusetts General a committee was appointed under the chairmanship of Dr. J. C. White. This committee * made plans for a combined laboratory and clinical study with

* The committee was composed of: Surgical: J. C. White, R. R Linton, F A Simeone, C. E Welch, and F. D Moore. Medical. R. S. Palmer, P. D. White, D. G. Loofbourow, C. S. Kubik, A. Butler, and J. H. Currens.

special reference to the effects of operation on blood pressure and other methods of treating this disease. With the aid of a generous grant from the Life Insurance Medical Research Fund it was possible to support professional assistants and to obtain the help of technicians and secretaries.

Dr. Kenneth A. Evelyn, formerly Director of Medical Research for the Royal Canadian Air Force and Assistant Professor of Medicine at McGill University, now Director of the Nuclear Physics Research Laboratory at McGill, was placed in charge of the Hypertension Laboratories during 1947 and 1948. Dr. Evelyn was selected because of his special training in objective statistical analysis and absence of any personal bias, as these patients had been neither selected nor operated upon under his direction. He also had outstanding qualifications as a physiologist to direct the studies before and after sympathectomy which were carried out in the research laboratories. When he returned to Montreal, his place was taken by Dr. William P. Chapman of the medical staff.

Under Dr. Evelyn's direction an elaborate system of study was devised for new patients and for the follow-up of patients who had already been treated (cf. Evelyn, Alexander, and Cooper, 1949). Two hundred fifty-seven cases submitted to thoracolumbar sympathectomy between 1939 and 1947 were studied. Another group of patients whose medical status was equivalent to that of the surgically treated patients, but who were not operated upon because of some reason other than their operative risk, were also collected for study. Most of the physiologic studies in this connection have been reported (Simeone and Vavoudes, 1948; Simeone and Ramirez, 1950). A further evaluation of the results of surgical and medical treatment of hypertension at the Massachusetts General Hospital has been recently published by Loofbourow and Palmer (1950). The remainder of the clinical studies from this hospital will be ready for publication in the near future.

If blood pressure alone is taken as an index, Evelyn *et al.* (1949) observed that of the first 100 cases five years after thoracolumbar sympathectomy 27 had died, only 8 had normal blood pressures, and 13 others a significant improvement. This represents a percentage of 21 having a prolonged reduction in blood pressure. In calculating these percentages, the deaths were included, thus giving a lower figure than the 42 per cent having lowered blood pressure quoted by Smithwick above. Smithwick has not included the patients who died during the period of follow-up in his evaluation of reduction in blood pressure and other evidences of improvement. If these are included, the results in our two series become comparable. The

as for nonhypertensive individuals. Only seriously damaged or nonfunctioning kidneys should be removed. The opposite kidney should be normal. It is inadvisable to remove the poorer of two involved kidneys. Since there are inadequate data concerning the late results of unilateral nephrectomy, and since the chances for improvement for a short time are slight (20 per cent, according to Smith, 1948), it seems best to recommend that unilateral thoracolumbar sympathectomy and splanchnicectomy be performed at the time of nephrectomy.

C. ADRENALECTOMY

Partial adrenalectomy was one of the first procedures to be tried in the surgical approach to hypertensive cardiovascular disease. A portion of both adrenal glands was removed with and without associated sympathectomy and splanchnicectomy. The results were not impressive. This may have been due to the removal of an inadequate amount of adrenal tissue. It is known that hypertension cannot exist in the absence of the adrenal cortex. The advent of replacement therapy has made possible a further trial of subtotal and even total adrenalectomy, alone or in combination with sympathectomy and splanchnicectomy. At present, there are no data of importance concerning this re-evaluation of adrenalectomy. One of us (R. H. S.) is exploring this matter in certain S. Group 4 cases (Table XXXI). It does not seem proper at this time to use this procedure in S. Group 1, 2, or 3 cases, since the prognosis for these patients is so satisfactory following sympathectomy and splanchnicectomy alone (Fig. 62). Subtotal or total adrenalectomy must be regarded as highly experimental at the present time.

VIII. Comments on the Surgical Treatment of Hypertension Based on Massachusetts General Hospital Study, 1945 to 1950

During the first decade of these studies all the operations on hypertensives which have been reported above were done at the Massachusetts General Hospital. In 1945 Dr. Smithwick left to assume his duties as Professor of Surgery and Head of the Department of Surgery of the Boston University School of Medicine and the Massachusetts Memorial Hospitals. In order to continue the study of hypertension at the Massachusetts General a committee was appointed under the chairmanship of Dr. J. C. White. This committee * made plans for a combined laboratory and clinical study with

* The committee was composed of: Surgical: J. C. White, R. R. Linton, F. A Simeone, C. E. Welch, and F. D. Moore. Medical. R. S. Palmer, P. D. White, D. G. Loofbourow, C. S. Kubik, A. Butler, and J. H Currens.

of definite renal impairment or for patients, particularly males, over 50 years of age, or for those with asymptomatic hypertension.

The policy of selecting hypertensive patients for sympathectomy at the Massachusetts General Hospital may turn out to be overconservative. Only 20 hypertensives have been operated upon in the last two years. This conservative attitude on the part of the medical staff is based on a much smaller series of cases than Smithwick's that he has cited above. While not a panacea, this method, which has significantly and enduringly reduced blood pressure in 20 per cent of cases, is not to be disregarded. Smithwick has presented data which indicate that sympathectomy has prolonged the life span of hypertensive patients significantly. It is not possible to confirm or deny this from the Massachusetts General data to date. To the group of internists and surgeons working there on this problem it would seem preferable at this time to accept Smithwick's evidence with an open mind and to continue with careful study of patients operated upon and of identical controls until more data have accumulated.

Another reason for the reduction in sympathectomies for hypertension at this hospital during the last few years is the increased interest in dietary and drug therapy, and patients have been diverted to this type of treatment for study. This will undoubtedly assume its proper place in the management of patients with hypertension, whether alone or in conjunction with sympathectomy, in the immediate future.

As previously mentioned, it is to be borne in mind that Dr. Smithwick's statistics are based on a far greater proportion of private patients than are found in the series of 100 five-year results evaluated by Evelyn *et al.* (1949) from which the conclusions in this section are drawn. The more well-to-do hypertensives can take better care of themselves after sympathectomy and may do better for this reason. The recently published article by P. D. White *et al.* (1950), based entirely on his private cases from the Cardiac Clinic of the Massachusetts General Hospital, seems to bear this out. Here we have a notable discrepancy between the results in two series of cases drawn from the files of the same hospital, the one from the public-ward records, the other exclusively from the private services Dr. Smithwick operated on the majority of the former and all of the latter. Dr. Paul White's findings corroborate Smithwick's views expressed in the first part of this chapter. These 50 patients had all suffered serious cardiovascular complications: left ventricular weakness and failure in 26; cerebrovascular accidents in 17; angina pectoris in 20, and myocardial infarction in 10. They were then followed over a three-year period and contrasted with a similar series not operated upon. Among the surgically treated cases

cases studied by the Massachusetts General Hospital Hypertension Laboratory were all ward cases operated upon and living in Massachusetts. The follow-up was complete. Such patients, however, might well respond differently from private patients, which constitute the great majority of Dr. Smithwick's series. Most of the latter came from far-distant places, and none were included in this study, whereas in Smithwick's survival statistics the mortality rates were calculated for the entire series. Approximately 1 out of 5 patients operated upon is living and improved, in regard to blood pressure, after five years. As Smithwick has shown, the blood-pressure response is not the only important, or even the most important, effect of sympathectomy on hypertension. Data from the Evelyn-Chapman study of the effects of operation upon the symptomatology are not quite ready for publication at this time. Genuine relief of headache does occur in a high proportion of cases, 85 per cent according to Chapman (personal communication).* Interpretation of the effects of operation upon symptoms, however, is more risky than the interpretation of the effects upon the blood pressure, which is a reasonably objective index.

At the present writing the general policy of the Medical Service at the Massachusetts General Hospital is to avoid operation for patients with K.W.B. Group 1 hypertension. Sympathectomy is recommended for the following varieties of hypertension: (1) Patients with K.W.B. Group 2 hypertension when medical follow-up suggests progression toward K.W.B. Group 3 in spite of medical and dietary treatment, or when the hypertension is accompanied by disabling headaches and other symptoms. (2) Selected patients with K.W.B. Group 3 hypertension who have disabling symptoms or who show no improvement or progression of the disease, despite medical treatment. The selection and results in this group have recently been described by P. D. White *et al.* (1950). (3) K.W.B. Group 4 hypertensives appear to fare better on medical treatment after sympathectomy than on medical treatment alone (Loofbourow and Palmer, 1950), and operation is recommended for these patients unless they show severe renal damage with progressive azotemia. Preliminary observations upon a small number of patients suggest that a measurement of the renal blood flow may be a useful index for selection (Simeone and Ramirez, 1950), and if this correlation withstands the test of time it should be possible to substitute simpler tests of renal function for it. Operation is seldom recommended in the presence

* Shenkin *et al.* (1950) have recently studied the cerebral blood flow in hypertensive patients before and after thoracolumbar sympathectomy. Their data suggest a decrease of the resistance within the cerebral circulation, which may explain the improvement in the cerebral symptoms and in the retinal blood vessels. The mechanism for this decrease in the cerebral vascular resistance remains obscure.

removed. A useless kidney can be removed and, in other cases, information regarding the role of the kidney in hypertension can be obtained by gross inspection and through the study of biopsy material.

The thoracolumbar technique appears to be the most useful operation. It should not be radical in nature or else the untoward physiological effects will outweigh the benefits of the procedure. As a rule, the sympathetic trunks should be removed bilaterally from T8 to L1, inclusive, together with the splanchnic nerves. In certain cases cardiac denervation seems indicated as part of the original procedure. In such patients total, or subtotal, thoracic sympathectomy appears to be advisable. In other words, one must be careful to select the most appropriate operation for the particular case. A more extensive procedure (total sympathectomy) is rarely necessary and should be performed in stages and for some particular reason. It seems inadvisable as a primary operation.

The selection of cases for surgery is extremely important. Early evidence indicates that carefully selected hypertensive patients will benefit from *appropriate* surgery. In proper hands the mortality is slight, the statistical chance of a worth-while result is good, and the untoward effects are not serious. A careful study of late results already indicates that life expectancy has been prolonged to a statistically significant degree in patients having continued hypertension with cardiovascular changes ranging from slight to severe (Groups 2 and 3, Smithwick classification, Table XXXI).

Other measures such as regulation of the patient's routine of life and the use of diets and drugs, which are also helpful, should not be neglected. The efforts of groups of individuals—physicians, surgeons, physiologists, and investigators—should be correlated and utilized to the best interest of the hypertensive patient. Since the cause of essential hypertension is unknown, all therapeutic measures must be regarded as more or less empirical in nature. Surgery should be employed where it has been shown to be most effective, i.e., in patients contained in S. Groups 2 and 3. It seems highly probable that the patients who will do best in the long run will be those who have the benefit of both surgery and medicine. It is becoming increasingly obvious that surgery should not be reserved as a last resort.

12 (24 per cent) had died within this period, one of intercurrent disease. Of the controls, 41 (82 per cent) had died. Of the survivors in the surgical series, 12 had blood pressure either within the normal range or reduced to a level of 150/100 or lower. While these blood-pressure figures are not significantly different from Evelyn's statistics, the survival rate and general medical status of these severe cases after operation is definitely more encouraging. The clinical result was reported as * "excellent or good in 11 and fair with definite, though not decided, improvement in 11; in 5 instances there was little or no change; 11 patients were worse, and 12 were dead. In contrast, among the medically treated controls, only 1 patient continued to be in good condition, 4 were in fair condition with some improvement, 4 were unchanged, and 41 were worse or dead." Our differences in interpreting results may therefore be accounted for, at least in part, by the types of cases examined.

While considerable progress has been made regarding the evaluation of the surgical treatment of hypertension since the second edition of this book, the question is by no means settled, and much work is still needed. It is natural that there should be some difference of opinion among physicians in general and even among the authors of this present edition As far as the Massachusetts General and the Massachusetts Memorial Hospitals statistics are concerned, there is no important divergence of opinion concerning the effect of sympathectomy on blood pressure. Smithwick has emphasized that increase of life expectancy is the most important criterion for judging results, while the physicians most concerned with this problem at the Massachusetts General Hospital are not yet prepared to accept unqualifiedly the statistical evidence that longevity is increased by sympathectomy. This may well be the case, and it is greatly to be hoped that this critical point will soon be established to the general agreement of all concerned.

IX. Summary

The present status of the surgical treatment of hypertension has been summarized. The three most useful procedures have been commented upon. Extensive denervation of the vascular bed is the most widely applicable maneuver. Operations which thoroughly denervate the splanchnic bed are the most useful. The exposure should include exploration of the adrenal glands and kidneys. In this way, adrenal tumors will be found and can be

* White, P. D, Dimond, E. G, and Williams, A "Follow-up study of one hundred private hypertensive patients with cardiovascular complications" *J. Amer. med Ass*, 1950, 143: 1311–1317, courtesy of American Medical Association, Chicago.

hibit inspiration, and expiration follows. There are other receptors in the same biological areas which induce inspiration if the alveolar ducts and atria have been overcollapsed."

In addition to this vagal innervation, which causes reflex stimulation of expiration and inspiration, there is a higher control in the plexuses of the aortic arch and carotid sinus, which, through pressor and chemoreceptors, acts in an accessory capacity to the main respiratory center in the medulla.

II. Neurosurgical Treatment of Bronchial Asthma

In the group of asthmas due to sensitization to foreign protein, the onset of the attacks is most likely caused by a humoral mechanism. These patients constitute the class which obtain the greatest relief from medical therapy. There is, however, a growing realization that a large number of asthmatics cannot be explained on this basis. In these, reflex spasm of the bronchi may play an important role. Some evidence for this rests on observations that psychic and emotional stimuli often lead to attacks.

However, as H. L. Alexander (1933) stated, we do not know whether the asthmatic paroxysm is "due to spasm of the bronchial muscles, to edema of the bronchial mucosa, or to hypersecretion of the bronchial glands." Alexander presented evidence that all three factors play a part and that each is activated by vagal stimulation. On this basis, destruction of the sympathetic pathways appears to be an unreasonable procedure.

The early literature, well reviewed by Phillips and Scott (1929), contains a number of accounts of partial sympathetic denervation of the lung, usually limited to stellectomy. Although a number of successful results were reported, many of these case reports contain such inadequate data and such a brief period of follow-up that they are of little value. Dr. F. M. Rackemann, formerly head of the Allergy Clinic at the Massachusetts General Hospital, has pointed out that in many asthmatics various nonspecific operations as well as acute infections often produce a good result, at least for a time. Sooner or later, however, the asthma returns.

Complete sympathetic denervation of a lung has been carried out by one of us in 4 patients who were studied in collaboration with Dr. Rackemann. The denervation was performed by removing the upper four thoracic sympathetic ganglia through a posterior approach in 3 patients and by paravertebral alcohol injection in the fourth. Ultimate results in these cases have not been impressive, and on account of them we have not planned further intervention along these lines.

From the modern physiological viewpoint, bilateral resection of the vagal connections with the posterior pulmonary plexus would appear to be

CHAPTER XIII

The Lung

I. Innervation

It has been shown in Chapter III that the anterior and posterior pulmonary plexuses receive their extrinsic innervation from the vagi and from the inferior cervical and upper four thoracic sympathetic ganglia. For the details of the neuroanatomy of the lung the reader should examine Fig. 14, which is reproduced from Braeucker (1927), and read the outstanding contributions of this investigator (1926*A* and *B*, 1933).

Phillips and Scott (1929) and Rienhoff and Gay (1938) have given clear descriptions of the nervous control of the human bronchial musculature and the secretion of its mucous glands. Apparently, the vagus carries constrictor fibers to the larger bronchioles, for Weber (1914) observed that stimulation of the distal end of the nerve resulted in constriction of the main bronchi and its paralysis in dilatation. A striking roentgenographic demonstration of this effect has been published by Francis (1929). It has been confirmed in man by Tucker (quoted by Kern, 1926), who observed a definite unilateral reduction of bronchial constriction through the bronchoscope after section of the left vagus. Dixon and Ransom (1912) claimed that stimulation of the upper thoracic sympathetic ganglia in animals commonly resulted in bronchodilatation on one or both sides.

The lung parenchyma is very insensitive to pain, so that intrapulmonary disease is never painful unless lesions involve the main bronchi, which are supplied by somatic vagal fibers, or the parietal pleura, which derives a rich supply from the intercostal nerves. Sympathectomy, therefore, has no effect on pain in pulmonary disease. Cough reflexes are mediated by vagal endings in the larger bronchi, which become progressively fewer in number in the smaller bronchioles.

Vasomotor control of pulmonary circulation is not very striking, as this is mainly adjusted to accommodate the output of the right ventricle.

The major role of the pulmonary nerves is the regulation of breathing. This has been so well described by Drinker (1948) that we cannot do better than quote his conclusions. "Vagal receptor endings are found at the beginning of the alveolar ducts and atria. Impulses from these nerves in-

to operate in the early stages of asthma in which there is evidence of reflex bronchospasm.

III. Control of Pain in Pulmonary Disease

As stated in Chapter VI, the pulmonary parenchyma and visceral pleura are insensitive (J. A. Capps and Coleman, 1932). It is only when disease spreads to the parietal pleura or the main bronchi and trachea that pain is felt. Morton, Klassen, and Curtis (1950*A*) have stimulated the mucosa of the lower trachea and primary bronchi through a bronchoscope and demonstrated that pain is referred to the substernal or parasternal area. In the case of disease involving the parietal pleura, nothing can be accomplished by sympathectomy, as the afferent fibers run in the intercostal and phrenic nerves, or over the brachial plexus in the case of the apical pleura. Pain from carcinoma in this area is one of the most difficult problems which the neurosurgeon may be called upon to relieve. In the superior pulmonary sulcus syndrome described by Pancoast (1932), the nerves at the base of the neck are infiltrated by the growth, resulting in severe pain in the shoulder and arm, a Horner's sign, and in addition often a hoarse voice and reduced movement of the diaphragm from paralysis of the recurrent laryngeal and phrenic nerves. Under these circumstances it is necessary to perform a very high section of the spinothalamic tract In painful conditions of limited extent where the lower thoracic pleura and its intercostal nerves are involved, posterior root section is a satisfactory operation. For a description of neurosurgical methods of dealing with these conditions, the reader should refer to the monograph on neurosurgical control of pain by White and Sweet (1952).

When bronchogenic carcinoma gives rise to an incapacitating cough reflex with accompanying pain, Morton, Klassen, and Curtis (1950*B*) have shown that this can be relieved by cutting the ipsilateral vagus nerve beneath its recurrent laryngeal branch. They have performed this operation on 25 cases with 17 successful long-term results.

Metycaine block of the stellate ganglion was reported recently by Bageant and Rapee (1947) in 2 patients with pulmonary embolism. In both cases the patients were relieved dramatically of their chest pain and dyspnea. One of them had a second pulmonary embolus one week after the first. He himself requested a block for this episode and again experienced dramatic relief from it. He died nine days later from a third pulmonary embolus. The authors suggested that the stellate block may not only relieve pain by interrupting afferent pathways from the lung but may also interrupt any

the most promising method of interrupting bronchospasm of neurogenic origin. This operation was first performed by Phillips and Scott (1929). It has been given a thorough trial by Rienhoff and Gay (1938), who have performed a bilateral resection of the posterior pulmonary plexus in 10 severe asthmatics. In this operation a certain number of sympathetic rami must be divided in addition to all the vagal connections. When the results were reported two years after the last operation, 4 remained free of attacks and had been able to return to work; 4 more had occasional mild attacks of asthma, all of which were amenable to control by medication; 1, who had improved for three months, had then succumbed to cardiac failure; and only 1 had shown no improvement. In answer to a recent inquiry Dr. Rienhoff has stated that he has been able to obtain gratifying improvement in about 40 per cent of asthmatics who are free of such irreversible changes as chronic bronchitis, bronchiectasis, or myocardial damage. "Some of the results have been simply brilliant and others discouraging. . . . It is most difficult indeed to get a patient in whom the element of bronchial spasm is solely responsible for the asthma." He therefore recommends the operation very guardedly. All candidates for surgery must have a preliminary psychiatric examination, as there is such a large functional element in this disease. Blades *et al.* (1950), who have denervated a single lung at the pulmonary hilum in 32 cases and performed the operation on both sides in 6 others, have had results very similar to Rienhoff's. They conclude that the dramatically beneficial results, on the one hand, and the failures, on the other, present a bewildering outcome following this empirical procedure.

We have had but a single experience, and in that patient only a unilateral denervation was performed. Its unsuccessful result cannot fairly be held against the method, since it is known that there may be some bilateral innervation of each lung.

In summarizing the work that has been done on bronchial asthma, it appears that sufficiently radical resections of the sympathetic rami have now been performed to give a fair indication of the value of these operations. In the face of their inconsistent results, it does not seem that sympathectomy has anything to offer in the treatment of this condition. On the other hand, total resection of the pulmonary vagal branches has some valid physiological and clinical backing. The results of Rienhoff and Gay and Blades are sufficiently impressive to deserve continued study and a wider trial. As the procedure carries a minimal risk, it seems a pity that the allergists cannot be persuaded to give qualified surgeons an opportunity

CHAPTER XIV

Gastrointestinal Tract

I. Nervous Control of the Gastrointestinal Tract

As pointed out in Chapter IV, it has long been known that the antagonistic action between the sympathetic and parasympathetic divisions of the autonomic nervous system, which regulates other forms of visceral activity, is less clear cut in the digestive tract. The essential mechanism that controls digestion lies in the intrinsic plexuses of the gastrointestinal canal. Secretory activity of the intestinal mucosa, the pancreas, and biliary glands is largely under local or chemical control. There is, however, evidence to show that the activity of the digestive tract is reduced during periods of intense emotion, when there is a generalized outburst of sympathetic impulses. It is of interest to recall that Lister (1858) was one of the first to bring out the inhibiting action of the sympathetic system on peristalsis, which he demonstrated by passing an electric current through the lower thoracic spine and observing that with a certain strength of current "the 'hemmung' action came into play and the intestines became relaxed and motionless." Lister records that he * "found the best mode of proceeding was to remove the skin and two layers of muscles from the abdomen of a rabbit, leaving the peritoneum and one layer of muscles, which are quite transparent enough to enable you to see any movements of the intestines, without the complication that the action of the air upon them involves."

There is much more physiological evidence than was formerly realized in favor of an antagonistic action of the thoracolumbar and craniosacral system in the control of the digestive processes. For example, when the sympathetic centers in the hypothalamus are stimulated there is a reduction in gastric tone and increased secretion of mucus, whereas when the anterior parasympathetic areas are excited there is a tendency to increased secretion of acid (Heslop, 1938; Sheehan, 1940). In 1941, when the last edition of this book was published, it was known that the sympathomimetic drugs ephedrine and Benzedrine delay gastric emptying, whereas the

* "Eight letters of Joseph (Lord) Lister to William Sharpey," by C. R. Rudolf, *Brit. J. Surg.*, 1932, 20: 145–164, courtesy of John Wright & Sons, Ltd., Bristol, England.

possible reflex spasm in the pulmonary and coronary blood vessels. Faxon *et al.* (1951) have reported similar favorable results. Of their 4 patients, relief of chest pain and dyspnea was very definite in 3 when the stellate block was carried out within the first few hours, whereas in the fourth case little improvement was noted when the injection was delayed.

and Owens (1943). Since that time additional reports of progress have been made by Dragstedt (1946) and Dragstedt, Harper, Tovee, and Woodward (1947). F. D. Moore *et al.* (1946), Grimson, Taylor, *et al.* (1946), and many others have reported early results.

In their writings to date Dragstedt and his associates have stressed the use of vagectomy in cases of refractory and complicated ulcers. Most of their subjects have been men with long-standing duodenal ulceration with or without previous surgery. They have also stressed the effect of this operation on the first period of gastric secretion, namely, that of interdigestive or continuous secretion. To obtain data on this matter, they collected gastric juice for twelve-hour periods from 9:00 P.M. to 9:00 A.M. by continuous suction, the stomach having been emptied and washed out prior to the collection period. The average findings for at least three such periods of observation prior to operation in 10 patients with refractory ulcers who had had no previous surgery were as follows: volume, 821 cc; free acid, 47 units; and total acid, 66 units. Following operation, the corresponding values were 335 cc, 15 units, and 46 units. In 9 cases of complicated ulcers the findings before and after vagectomy were similar. Some of these patients were obstructed, and a gastroenterostomy was also performed; others had had previous gastric resections or gastroenterostomies. In the discussion of the paper in which these results were reported, Grimson indicated that the twelve-hour night-secretion volumes in his series of 18 cases were reduced from an average of 946 cc before operation to one of 342 cc after operation. The acidity expressed in terms of pH was changed from an average of 1.72 before to 3.55 after vagectomy. These findings are of interest, not only because they indicate at least one clear-cut physiologic effect of the operation, but also because they cast additional light on the explanation of continuous gastric secretion.

Recently Ivy (1941), in an excellent discussion of the mechanisms of gastric secretion, indicated that the nature of the stimuli that give rise to the continuous secretion of gastric juice is uncertain. He stated that some patients, particularly those with a duodenal ulcer, manifested a hypernormal continuous secretion, i.e., the stomachs continue to secrete a copious quantity of acid juice after emptying. He suggested that this might be due to the production of histamine by an irritated mucosa, since atropine in relatively large doses does not abolish abnormal continuous secretion, whereas it has a significant effect on normal gastric secretion, as shown by Keefer and Bloomfield (1926).

In addition to the effect of vagectomy on the first period of gastric secretion, it seems probable that certain aspects of the second are favorably af-

parasympathetic stimulant Mecholyl accelerates; insulin increases gastric motility by raising vagal tone, and this response is abolished by atropine. Hartzell (1929) had observed in dogs that, when the entire vagal supply was sectioned in the thorax, there was a marked reduction of free and combined acid.* Psychic secretion of gastric juice was entirely eliminated. However, when Vanzant (1931) re-examined Hartzell's dogs two years later, he found acid curves which were practically as high as before operation, although at autopsy he saw no evidence of nerve regeneration. It is now established that total interruption of vagal impulses abolishes gastric secretion on psychic stimulation by the sight, smell, or taste of food (Pavlov, 1910), that hunger contractions are eliminated (Grossman and Stein, 1948), and that peristaltic activity of the resting stomach is likewise reduced (F. D. Moore *et al.*, 1947).

II. Treatment of Motor and Secretory Disorders

A. PEPTIC ULCERATION

In recent years reports of experiences with resection of the vagus nerves to the stomach in the treatment of peptic ulcer have appeared in the literature. The early results seem encouraging and suggest that vagectomy † may prove to be a useful adjunct to other measures available for the management of this disorder. A widespread interest has developed, and it is to be expected that the possibilities of this therapeutic measure will be explored in many clinics and that the literature on this subject will increase considerably in the next few years. As with everything that is new, the test of time will have to be applied before a final evaluation of results can be made.

Perhaps it is not quite correct to refer to vagectomy as a new procedure. Physiologists have been familiar with it for many years and have studied its effect on gastric function in great detail. One of the earliest references to its application in man is a report by Pieri (1932*C*). He performed bilateral subdiaphragmatic resection of the vagus nerves in 14 patients for the relief of gastric disorders, and stated that the operation was well tolerated and did not cause appreciable untoward incidents. The report that stimulated current interest in this matter was that of Dragstedt

* An interesting historical review of denervation of the stomach has been published by Small (1947). According to this account, the first observation that gastric secretion can be reduced by vagectomy dates back one hundred and twenty-five years to an experiment reported by Benjamin Brodie (1814) before the Royal Society of London. In the intervening years prior to Dragstedt's work, many investigators studied the effects of gastric denervation. Incomplete denervation, inadequate methods of recording its effects, and many other variables account for the bizarre and often conflicting results which were reported

† As an actual section of the vagus nerve is removed in these operations, we prefer the term "vagectomy" to "vagotomy."

that the antral factor in man, presumably a histamine-like substance if not histamine, the vagal factor, presumably acetylcholine, and the sympathetic factor, presumably an adrenaline-like or sympathin-like substance, not only play independent roles in gastric secretory mechanisms but also may potentiate one another.

In addition to these reported changes in gastric secretion, an alteration of gastric and intestinal motility is noted, particularly in the immediate postoperative period. This is evidenced by a delay in the initial as well as the total emptying time of the stomach. Its tone and reactivity are likewise decreased. These changes become less marked in the course of months and are rarely attended by symptoms of consequence. Whether these motility changes have any beneficial effect on the healing of peptic ulceration is not known. It is conceivable that a decrease in the tone and contractility of the smooth muscle of the stomach wall would have a favorable effect upon the circulation of the mucosa and perhaps render it more resistant to hydrochloric acid and pepsin

Grimson, Taylor, *et al.* (1946) believe that although changes in secretion and acidity are important, the most pronounced and consistent change produced by vagectomy is the decrease in motility of the stomach. On the other hand, Dragstedt and Schafer (1945) point out that in experimental animals in which gastric juice is allowed to be in contact with the intestinal mucosa when the alkaline duodenal secretion has been shunted distally (as in Mann-Williamson dogs), ulcers regularly develop. In these animals the motility factor has probably not been materially altered. In almost all reported cases the relief of symptoms, particularly pain, has been dramatic, immediate, and persistent. Nearly all ulcers have healed promptly. The effect of operation has so far been particularly gratifying in the group of troublesome cases in which gastrojejunal ulcerations have developed following gastric resections. The relief from pain is of interest since there is no evidence that pain pathways have been divided, as judged by postoperative balloon-distention observations. Pain is still perceived in response to stimulation of the esophagus, duodenum, and jejunum (F. D. Moore *et al.*, 1946) and when hydrochloric acid is introduced into the stomach (Dragstedt, 1946). It is therefore probable that relief of pain is due to either decreased acidity or motility. Since the hydrochloric acid levels may still be quite high after vagectomy, particularly in response to chemical stimuli, it is possible that decreased motility is the more likely explanation for pain relief following this operation and that reduction in acidity or the shunting of acid away from the ulcer is the probable explanation for pain relief following subtotal gastrectomy.

fected. This period may be divided into three phases—the cephalic, the gastric, and the intestinal. The first is known to be under the control of the vagus nerves. Stimuli such as sight, smell, taste, and thought of food result in gastric secretory activity mediated by the parasympathetic nervous system. Certain other stimuli, particularly some of an emotional variety, may cause increased vagal activity and acid secretion. There is no reason to doubt that the secretory response to these stimuli is inhibited by vagectomy. Thus, an over-all effect of this operation is to reduce both continuous and intermittent gastric secretion of neurogenic origin. Its efficacy in the treatment of some duodenal ulcers may depend on the extent to which the first period of gastric secretion, the cephalic phase of the second period, and other neurogenic or psychosomatic mechanisms enter into the problem at hand. It is true, however, that in some ulcer patients there is little evidence of an abnormality of neurogenic secretory mechanisms. Whether there will be any great effect on either the gastric or the intestinal phase of the secretory process awaits further study. These are thought to be largely under the control of chemical substances of a histamine-like nature.

After vagectomy a response to histamine or caffeine still persists, although in some cases a reduction has been noted following histamine, as pointed out by Grimson, Taylor, *et al.* (1946). Stein and Meyer (1948) report a marked reduction in the secretory response to histamine, whereas Schoen and Griswold (1947) find no significant change and believe that the histamine effect is independent of the vagus innervation. Different methods for studying gastric secretion were used by these two sets of authors, the former employing continuous suction and the latter intermittent aspiration with phenol red as an indicator to enable them to estimate emptying and secretory rates. They believed that this technique was more accurate than continuous suction, and the differences observed might possibly be explained on this basis. On the other hand, most observers use continuous suction, and the majority have noted a material reduction in the secretory response to histamine after resection of the vagus nerves. If this is so, it suggests that the presence of acetylcholine, the chemical mediator of parasympathetic impulses, potentiates the action of histamine. Stein and Meyer refer to evidence reported by Necheles *et al.* (1938) and by J. S. Gray and Ivy (1937) indicating that this is the case. It therefore would not be surprising if, after resection of the vagus nerves, the secretory response to histamine was decreased It is apparent from the observations of Wangensteen (1945) that adrenaline potentiates the action of histamine. There is evidence also that, in low concentration, adrenaline potentiates the action of acetylcholine (Burn, 1945). In other words, it is conceivable

circumstances under which vagectomy may be employed to be as follows: (1) For the relief of gastrojejunal ulceration following gastric resection in which at least the distal half of the stomach including the antrum has been removed; also following more radical gastric resections. The use of vagal resection in the treatment of gastrojejunal ulceration following gastroenterostomy is questionable, particularly in patients with high acid levels, but is countenanced by some. (2) Vagectomy may be used in combination with gastroenterostomy as a primary procedure in poor-risk patients or in cases where the local situation makes management of the duodenal stump hazardous and constitutes a contraindication to gastric resection. As indicated above, this combined procedure is preferred more or less routinely by Dragstedt and also by Crile, Jr. (1948).

Vagectomy is contraindicated in the treatment of perforation or hemorrhage. It should not be used as the sole procedure for treating peptic ulcer. In fact, in the surgical management of gastric ulcers, procedures other than gastric resection should rarely be used—because of the unavoidable diagnostic error of about 10 per cent in differentiating between benign and malignant ulcers—with the possible exception of juxtaesophageal lesions. In these cases the alternative approaches are total gastrectomy with excision of the ulcer or subtotal gastrectomy leaving the lesion in place.

At the present time it is our feeling that subtotal gastrectomy is regarded by most surgeons as the operation of choice for duodenal ulcer. This should include removal of the lower 75 per cent of the stomach with all of the antrum and lesser curvature, as advocated by Wangensteen. Most surgeons also prefer to use a short loop retrocolic gastrojejunostomy for restoration of continuity. This procedure has had an extensive clinical trial over a much longer period of time than has vagectomy. Consequently, until longer follow-up data are available, it has seemed best to suggest that vagectomy combined with posterior gastroenterostomy be used as an alternate to subtotal gastrectomy, and vagectomy alone be utilized following failure of subtotal gastrectomy.

It is realized that time may prove vagectomy in combination with other procedures to be superior to subtotal gastrectomy as a primary maneuver. One of us (R. H. S.) has been studying the effect of various operations and combinations of procedures upon the acidity of the gastric contents of both animals and humans. Early observations (Smithwick and Kneisel, 1950) suggest that resection of the vagus nerves combined with removal of the lower 50 per cent of the stomach has a uniformly profound effect upon the acidity of the gastric contents. Achlorhydria under fasting conditions and in response to stimulation by insulin or peptonized beef broth is the rule. In

for at least ten years in order that the results may be compared with those following other operations, particularly subtotal gastrectomy. While it is true that most recurrent ulcers develop within the first year or two after operation, a long follow-up is necessary to permit a sound evaluation of any therapeutic measure for peptic ulcer.

Whether one favors the combined procedure of vagectomy and gastroenterostomy over subtotal gastrectomy on the basis of early evidence depends to a large extent upon one's philosophy regarding the purpose of surgery for peptic ulcer. It is Dragstedt's (1950) belief that hypersecretion of hydrochloric acid owing to overstimulation of the vagus nerves is the important abnormality. Following resection of the vagi, this hypersecretion of the fasting stomach, which is evidenced by the milliequivalents of free acid and total output of gastric juice per unit of time, is reduced to well within the normal range. On the other hand, achlorhydria following vagus resection alone or combined with gastroenterostomy rarely develops either under fasting conditions or after the ingestion of food and stimulation by histamine. That it is necessary and desirable to reduce the output of hydrochloric acid to the point of achlorhydria or something closely approximating it, even after stimulation by histamine, is the thesis of another school of thought which is sponsored by Wangensteen and his associates (1945) and supported by abundant experimental and clinical data. The old dictum, "no acid, no ulcer," still holds until proved erroneous. It is true, however, that resection of the vagus nerves results in a profound and prolonged effect upon the tone and motility of the smooth muscle of the stomach wall in addition to its effect upon acidity. In this respect it differs from subtotal gastrectomy It is possible that this effect is important and may contribute to the abolition of the ulcer diathesis and permit ulcer patients to tolerate more acid than those who have been subjected to subtotal gastrectomy, which is not followed by decreased gastric motility. The reduction in tone and motility might have a favorable effect upon the vascular factor in the ulcer diathesis, which so far has defied evaluation. In any case, there are those who hold that decreased gastric motility is an important therapeutic effect. This has been repeatedly commented upon by Grimson, and recently Grimson, Lyons, and Reeves (1950) have re-emphasized this effect in a discussion of the early results of the treatment of peptic ulcer with orally administered Banthīne, a ganglionic blocking agent.

Realizing that all therapeutic measures have been directed toward the reduction of free hydrochloric acid and being of the school of thought that favors the reduction of acid not only to within the normal range but to the point of achlorhydria or something closely approaching it, we conceive the,

vagectomy together with gastroenterostomy was performed more often than any other operation. The early results of vagectomy for gastrojejunal ulcers are quite satisfactory. It would be helpful to divide these cases into two groups, those with previous gastroenterostomies and those with previous

TABLE XXXVII

Early Results of Vagectomy for Duodenal Ulcer *

Operation	*Number of Cases*	*Satisfied, Per Cent*	*Not Satisfied, Per Cent*
Transthoracic vagectomy	371	81	19
Subdiaphragmatic vagectomy	370	86	14
Subdiaphragmatic vagectomy and gastroenterostomy	1046	96	4
Subdiaphragmatic vagectomy and gastric resection	353	95	5

* These data were derived from the report of the Subcommittee on Vagectomy, American Gastroenterological Association, Apr. 29, 1950.

TABLE XXXVIII

Early Results of Vagectomy for Gastrojejunal Ulcer *

Operation	*Number of Cases*	*Satisfied, Per Cent*	*Not Satisfied, Per Cent*
Transthoracic vagectomy	148	86	14
Subdiaphragmatic vagectomy	102	93	7

* These data were derived from the report of the Subcommittee on Vagectomy, American Gastroenterological Association, Apr. 29, 1950.

resections. It would also seem wise to subdivide the cases which have had vagectomy combined with gastric resection into at least two categories, since it is the impression of one of us (R. H. S.) that the early clinical results have been better in cases in which not over one half of the stomach has been removed than in those in which the resection has been more radical. It would appear that the smaller the gastric remnant the more frequent are residual symptoms attributable to this, both in patients who have had vagectomy performed and in those who have had very radical resections without added denervation. It will be important to accumulate data regarding the results of gastroenterostomy and gastric resection alone to compare with those following vagectomy alone and in combination with those two procedures. The future reports of the Subcommittee on Vagectomy will be of great interest and value.

response to histamine the acidity of the gastric contents is greatly reduced in the immediate postoperative period, an effect which appears to become more marked with the passage of time. The effect of this combined procedure on gastric acidity is much greater than that of vagectomy combined with posterior gastroenterostomy. It also seems to have as great or an even greater effect than does subtotal gastrectomy upon the acidity of the gastric contents. The early clinical results likewise seem better than those following subtotal gastrectomy, in that the unpleasant side effects, such as distress after eating owing to the small gastric remnant, dumping syndromes, failure to gain weight, and the need for eating frequent small meals, are much less common.

In the immediate postoperative period we have had much less difficulty with delayed emptying of the stomach after vagectomy combined with resection of the distal half of the stomach than after vagectomy combined with posterior gastroenterostomy. Not much, if anything, has been published about the results of partial gastrectomy combined with vagectomy. Colp *et al.* (1948) have compared the effect of subtotal gastrectomy combined with vagectomy upon gastric acidity with that of subtotal gastrectomy alone. They found the combined procedure to have a greater effect upon the acidity of the gastric contents than subtotal gastrectomy alone. There is also an increasing amount of evidence to show that satisfactory clinical results have been obtained in a high percentage of cases in which vagectomy was performed for gastrojejunal ulcers which had developed after subtotal gastrectomy. Time alone will tell whether these alternate procedures will supplant subtotal gastrectomy as the operation of choice for duodenal ulcer.

The best summary available at the present time of the early results of vagectomy alone and combined with other procedures is the report of a Subcommittee on Vagectomy of the American Gastroenterological Association which was presented at their annual meeting Apr. 29, 1950 The material consists of data, collected from various surgeons throughout the United States, which were pooled in order to give an adequate number of cases for analysis. The operative mortality for the various procedures was low, averaging about 1.8 per cent There was no statistically significant difference in the rates for different operations. The follow-up period averaged one and a half to two years, which, of course, is too short a time to permit final conclusions. Data regarding the results of the various operations which have been discussed have been taken from this report and summarized in Tables XXXVII and XXXVIII. The results were judged according to whether the patient was satisfied or not. A survey of these tables indicates that the combined procedures have given the best early results, and that

C. CARDIOSPASM

Knight (1934) and Ferguson (1936) were able to produce a condition similar to human cardiospasm in cats and monkeys by cutting the thoracic vagi at a high level just beneath the origin of the recurrent laryngeal nerves. Following this experimental production of cardiospasm in the vagectomized cat and its relief by sympathectomy, Knight (1935) and Knight and Adamson (1935) submitted 3 cases of achalasia of the esophagus with cardiospasm to sympathetic denervation, resecting the left gastric artery and vein with the plexus of sympathetic nerves that innervate the region of the cardiac sphincter. A fourth case in which the result appeared to be encouraging was reported by Meade (1939). A cure of esophageal spasm of neurogenic origin at the level of the cricoid cartilage by resection of the superior cervical sympathetic ganglion has also been reported by Lambert Rogers (1935). In addition, an unusual instance of neurogenic achalasia with early dilatation of the lower esophagus following vagectomy for marginal ulcer has been reported by Moses (1947). This was treated along the lines suggested by Knight and Adamson and cleared up after a number of paravertebral blocks of the celiac ganglia and splanchnic nerves. Fifteen other experiences with sympathectomy in typical achalasia have been collected by Ochsner and DeBakey (1940*B*). The results on the whole were not impressive, and it is today generally agreed that direct surgical procedures on the dilated esophagus, which are now possible as a result of technical improvements in the transthoracic approach, are far more effective.

D. PYLOROSPASM

A recent article by Luzuy (1946) contains the interesting suggestion that pylorospasm in infants is of neurogenic origin and can be treated by repeated procaine block of the splanchnic nerves. No confirmatory evidence is available.

E. BILIARY AND PANCREATIC SECRETION

Bainbridge and Dale (1905) first showed that the gall bladder and sphincter of Oddi have an opposed innervation. In recent years French surgeons in Lyons have obtained evidence by cholecystography and manometric recordings of pressure in the gall bladder and biliary ducts which indicates that a preponderance of sympathetic activity leads to stasis of bile. Biliary pressure can be raised experimentally by vagal stimulation, and better emptying of the gall bladder can be secured by splanchnicectomy

B. CHRONIC ULCERATIVE COLITIS

Dennis *et al.* (1948), at the University of Minnesota, have presented a carefully prepared report of the results of bilateral vagectomy (usually performed by the transthoracic route) in 25 patients with idiopathic ulcerative colitis. This operation was first tried in the case of a young woman who had previously had a total colectomy and five sixths of her ileum removed. Severe involvement of the remaining bowel failed to respond to all known conservative measures. Vagectomy with revision of her ileostomy resulted in striking improvement over a period of eighteen months. Of 16 patients treated by vagectomy alone, 6 became asymptomatic, 4 greatly improved, and 6 were listed as failures. Despite an early favorable response, reactivation of the disease with diarrhea and bleeding took place in 3 of these. The response was most pronounced and prompt in cases in which there was no extreme fibrosis of the intestinal wall. The patients gained weight, and the number of daily stools decreased. Postoperative studies disclosed definite signs of improvement in the mucosa on proctoscopy. The abnormal roentgen appearance of the colon tended to return toward normal with a tendency to less spasm after division of the vagi. Blood, pus, or mucus in the feces was found with less frequency in half the cases, although none were completely free of these constituents In addition to slower emptying of the stomach, transit of barium through the ileum and colon was considerably slowed. The authors believe that one of the chief factors responsible for the improvement is the reduction in reflex motor activity and vasodilatation on emotional stimuli. The flushing and engorgement of the rectal mucosa, sometimes accompanied by petechial hemorrhage, which they observed through the proctoscope to follow discussion of disturbing topics preoperatively was abolished after vagectomy.

On the basis of this experience it is reasonable to consider vagectomy as an experimental procedure, which may prove of possible benefit in early cases of ulcerative colitis, and not as a proved therapeutic measure. It has not hitherto been recognized that the vagus nerves innervate the rectum and descending colon, where ulcerative colitis often starts and is usually most severe. Any effect of vagectomy in these areas would necessarily be indirect. If vagectomy is done for ulcerative colitis, and especially in advanced cases, it is essential to bear in mind that spontaneous remission is not uncommon in this disease and that the patient is subject to exacerbations with hemorrhage and perforation and to the development of malignant changes in the affected part of the colon.

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(Mallet-Guy and Guillet, 1943 and 1944; Poilleux and Guillet, 1947). These experiments have been corroborated in this country by F. E. Johnson and Boyden (1943). The advantages of this neurosurgical procedure over standard operations to drain the biliary passages remain to be confirmed.

Similarly Mallet-Guy, Feroldi, and Reboul (1949) have recently reported that drainage of the pancreatic ducts is inhibited by splanchnic impulses and that pancreatitis can be produced by stimulation in animals. They have therefore advocated left splanchnicectomy in the treatment of chronic pancreatitis. Similar suggestions have been made by Popper (1933) and Reyes (1945).

A very recent finding of Ayers, Stowens, and Ochsner (1950), that the severe nutritional changes and respiratory lesions associated with congenital fibrocystic disease of the pancreas can be improved by sympathetic denervation of the gland, may be of the greatest importance in this fatal disease of children. They have reported spectacular results following splanchnic block with procaine and complete right-sided splanchnicectomy in 4 cases. The diagnosis was established by clinical picture, fecal examination, and absence of the pancreatic enzyme trypsin in the duodenal contents. Increase in trypsin content in the duodenum was clearly evident after chemical or surgical denervation, as was the amount of bronchial secretion. A fifth child died from cardiac arrest in the course of the operation. The four survivors have shown an immediate general improvement, especially in regard to gastrointestinal and pulmonary symptoms. While the improvement in the digestive mechanism may result from an increase in blood supply of the pancreas, the authors believe that the improvement in pulmonary pathology takes place too soon to be explained by an increased absorption of vitamin A. They therefore hypothecate that denervation of the pancreas interrupts an abnormal reflex arc which adversely affects the lungs as well as the gastrointestinal tract. It will be a matter of the greatest interest to see if this preliminary hopeful report is confirmed by lasting improvement of digestive function and the arrest or reversal of the secondary bronchiectasis. Of equal academic interest will be the confirmation of the hypothesis that abnormal reflexes from a diseased viscus may be the cause of serious pathological changes in others.

Pancreatic secretion was formerly regarded as being largely under hormonal control (see p. 89), and it remains to be confirmed whether neurophysiological methods have a significant therapeutic effect. As far as the internal secretion of the pancreas is concerned, attempts have been made by de Takats and Cuthbert (1933) to control the hyperglycemia of diabetes by splanchnic and adrenal denervation, but these efforts have not

been successful. Simeone and Vavoudes (1948) have recently found that sympathetic denervation of the human pancreas does not greatly increase the sensitivity to insulin, as is the case in experimental animals.

F. MEGACOLON

When the nervi erigentes, which carry the pelvic parasympathetic impulses to the rectum and lower colon, are paralyzed, a condition similar to human megacolon is produced in the experimental animal (Adamson and Aird, 1932). Ivy (1938) has recorded further observations which point in the same direction. Similar changes are sometimes seen in man after destruction of the sacral end of the spinal cord or the cauda equina. White *et al.* (1940) studied a tabetic patient with a huge dilatation of the entire colon, which reacted in all respects like the atonic tabetic bladder.

There is experimental evidence that stimulation of the lumbar colonic nerves leads to contraction of the sphincter ani internus and relaxation of the detrusor muscle of the colon in the dog (Learmonth and Markowitz, 1929 and 1930) But from data obtained in a well-planned investigation of defecation in man, Denny-Brown and Robertson (1935) have concluded that the mechanism which controls evacuation of the bowel is mediated entirely through the lower sacral segments of the spinal cord and its peripheral plexuses. There is no evidence that the sympathetic supply (superior hypogastric plexus) plays any part in these visceral responses.

After studying the activity of the large bowel in different lesions of the nervous system, White, Verlot, and Ehrentheil (1940) found that the smooth muscle of the rectum and colon reacts to distention in a manner quite similar to skeletal muscle after a sudden stretch; in other words, the peristaltic rush waves which sweep the contents of the colon down into the rectum are a reflex contraction of smooth muscle and correspond to the reactions which have been so thoroughly studied in the bladder (see Chap. XV). As such, they respond after injury in much the same manner as the reflexes of skeletal muscle. This evidence was obtained by recording the pressure curve during slow filling of the colon with warm water. When so recorded, the colonmetrogram closely resembles the cystometrogram, except that the colon holds a three to four times greater volume of fluid. From a study of the changes in bowel activity after lesions at various levels of the nervous system, it is clear that reflex activity and ability to empty the colon effectively persist until the reflex centers in the sacral cord, the cauda equina roots, or the pelvic nerves have been injured. Determinations of intracolonic pressure-volume relationships (unpublished data) were also made before and after bilateral lumbar ganglionectomy and combined lum-

bar ganglionectomy and splanchnicectomy in a number of subjects with normal bowel function.* After sympathetic denervation of the normal rectum and colon, no alteration was visible in either the basic tone of the bowel, its peristaltic activity, or its sensory acuity. These experimental findings give little support for treating congenital or acquired dilatation of the colon by sympathectomy. Nevertheless, there has been some evidence of clinical improvement in patients in whom the existence of a neurogenic factor is indicated by a thorough evacuation of the dilated colon under diagnostic spinal anesthesia (W. J. M. Scott and Morton, 1930).

At the time the previous editions of this book appeared, various forms of sympathetic denervation of the colon were being advocated for the uncomplicated early cases of congenital megacolon or Hirschsprung's disease (1887). Experience favored sympathetic ganglionectomy, in which the first three lumbar ganglia were removed on both sides. Unfortunately, bilateral resection of the first lumbar ganglia in the male is likely to be followed by sterility † and, as Bargen pointed out in his discussion of Penick's (1945) paper, males predominate over females 5:1 in the sex incidence of this disease. Similar objections applied to Rankin and Learmonth's (1930) operation, in which the inferior mesenteric and superior hypogastric plexuses were excised. Adson (1937) and Leriche (1937*B*) had recommended cutting the splanchnic trunks beneath the diaphragm in addition to bilateral removal of the lumbar chains. For the more advanced cases and in those in whom sympathectomy had failed, colectomy was the only recourse.

The extensive bibliography on neurosurgical treatment of congenital megacolon and the results of these operations can best be obtained from the monograph of Midon (1944) and Penick's (1945) article. We are in agreement with Penick that sympathectomy has a very limited value in the treatment of congenital megacolon in children, and we are convinced that it is useless in the acquired variety in adults. Not only have the results of sympathetic denervation been far from consistent, even in the most favorable cases, but more conservative medical measures are now available for treating these children. For the more advanced resistant cases a safer and more satisfactory operation, based on an entirely new principle, is supplanting colectomy.

For medical treatment Law (1940) proposed the use of acetyl-beta-methylcholine bromide, accompanied by such simple auxiliary aids as liquid

* Patients with Raynaud's disease and essential hypertension

† Resection of the first pair of lumbar ganglia, as is the case with resection of the hypogastric nerves, often causes sterility in the male (see p. 399), because the fibers which pass through these ganglia stimulate peristalsis in the vasa deferentia and ejaculation

petrolatum and an occasional enema until the evacuation habit is established. This drug can be given by mouth, and its prolonged peristaltic action with minimal toxicity makes it more effective than the other acetylcholine derivatives which have long been known to stimulate intestinal action. Law recommended an initial dose of acetyl-beta-methylcholine bromide of 0.1 gm administered a half hour after breakfast and increased after three days to 0.2 gm. If necessary it may later be increased by giving a similar dose in midafternoon. Overdosage is indicated by diarrhea. When the dosage is found which produces one to two stools a day the patient is discharged, usually taking 0.2 gm of the drug each morning and from 1 to 2 tbsp. of the liquid petrolatum each evening, with instructions to use an enema in the event of constipation or distention. In Law's experience in the treatment of 6 children suffering from megacolon with acetyl-beta-methylcholine bromide and liquid petrolatum, the results were entirely successful.

In some children who have been resistant to this treatment good results have followed one or more therapeutic spinal blocks. Preliminary studies by Chapman (unpublished data), using the multiple balloon-kymographic recording system in the colon, indicate that propulsive contractions are increased which facilitate evacuation of its contents. In these cases spinal anesthesia should be carried up above the nipple line in order to include all the motor roots from which the splanchnic rami originate. When the spinal block is administered it is essential that no preliminary morphine be used, as Rowlands *et al.* (1950) have so clearly demonstrated that this causes intermittent spasms followed by relaxation in the small intestine. During this period propulsive contractions largely disappear. The action of atropine, similarly investigated by multiple balloons in the gut by Chapman *et al.* (1950), also leads to a striking decrease in propulsive contractions and to a slight diminution of "tone." The therapeutic use of repeated lumbar subarachnoid injections of procaine was first proposed by Stabins, Morton, and Scott (1935), and its value was further emphasized by Scott (1936) and by Telford and Simmons (1939), who demonstrated that in many young children normal bowel function may be restored without the need of surgical denervation. Telford and Haxton (1948) have recently reviewed the late results (two to nine years) of patients treated by repeated spinal blocks rather than by actual sympathectomy. Out of 12 children with an average age of seven years, 8 were found to have remained fully cured, 2 improved, and 2 showed no improvement. In the successful cases the parents noted that the children became more energetic physically and much brighter mentally. Lumbar sympathectomy had been carried out in

3 of the less successful cases, but in only 1 had there been any further improvement.

Children with the milder neurogenic variety of the disease are very likely to improve on treatment with one or other of the conservative measures just described. In those that fail, it is so doubtful that sympathectomy will bring about any added benefit that this operation has been largely abandoned. For the more advanced cases of the disease, where these conservative measures have failed, colectomy was formerly the only recourse. This operation in sickly, malnourished children carried a high mortality, and the results were not always successful, as proximal dilatation of the ileum often ensued.

For resistant cases of congenital megacolon an entirely new surgical treatment has recently been developed by Swenson, Rheinlander, and Diamond (1949) from the Children's Hospital in Boston. As a result of motility studies of the dilated large bowel with multiple recording balloons, it is their contention that the primary pathology is located not in the dilated hypertrophied colon but in the distal, nondilated rectosigmoid. They observed the progress of active peristaltic waves along the enlarged colon, but these failed to enter the narrow distal segment which exhibited increased tonus. This physiological defect appears to be the cause of chronic partial obstruction. The malfunctioning segment corresponds to the narrow irregular rectosigmoid visualized by X ray in which there is a remarkable absence of ganglion cells in the myenteric plexus on histological examination. At the time of this preliminary report, removal of the narrow irregular rectum and rectosigmoid by a special surgical technique had resulted in what appeared to be 33 complete cures and a single postoperative death. Within three months after operation the appearance of the large intestine had been restored to normal on fluoroscopic examination with barium enema, and it was possible to demonstrate normal colonic peristalsis by balloon studies

III. Alleviation of Pain from the Abdominal Viscera

The following evidence indicates that the sensory axons from the abdominal viscera run with the sympathetic nerves, primarily in the splanchnics: When these nerves are cut, Sheehan (1932) found that the sensory endings (Pacinian corpuscles) in the mesentery undergo degeneration; when stimulated by means of a bipolar electrode in the course of operation under local anesthesia, severe pain is produced. This is in the upper quadrant of the abdomen on the side stimulated and has the same low threshold and

short latent period as the twelfth intercostal nerve (White and Sweet, 1952). When Kinsella (1948) and Bentley (1948) mechanically stimulated penetrating duodenal ulcers with the abdominal wall completely desensitized by regional block, pain was likewise clearly felt in the upper abdomen. This disappeared after splanchnic infiltration. After unilateral splanchnicectomy duodenal balloon distention is no longer perceived on the side operated on, and even more strenuous distention no longer causes pain on either side after bilateral denervation (Bentley and Smithwick, 1940).

Because upper abdominal pain of visceral origin is so completely relieved after splanchnicectomy, it has been feared that acute inflammation in this area may go unrecognized and lead to disastrous results. Weeks, Ryan, and Van Hoy (1946) have reported painless perforation of a duodenal ulcer after combined splanchnicectomy and vagectomy, with death from peritonitis. Painless rupture of an ulcer or an inflamed appendix, however, is most unusual, as the moment inflammation spreads to the parietal peritoneum, pain is transmitted over somatic afferents in the intercostal nerves. Craig *et al.* (1950), who have followed a large series of patients submitted to extensive thoracolumbar sympathectomy for hypertension at the Mayo Clinic, have been unable to discover any serious complications of this sort.

That the vagi carry no pain-bearing afferent fibers below the diaphragm has been proved by B. Cannon's (1933) experiments with buried electrodes in animals and by Grimson, Hesser, and Kitchin (1947) in man. The latter observed at operations under spinal anesthesia that, when the vagi were stimulated beneath the diaphragm, no sensation was aroused, but on stimulation 3 in. above, pain was referred to the neck. Cessation of ulcer pain after vagectomy is brought about by reduction of gastric peristalsis and acidity, as two of Grimson's patients still experienced pain from strangulation of a Meckel's diverticulum and from cholecystitis after vagotomy, and F. D. Moore, Chapman, Schulz, and Jones (1947) found no alteration in tolerance to balloon distention. Grossman and Stein (1948) have investigated the pain of hunger contractions and found that it is relieved both by splanchnicectomy and vagectomy. The former interrupts the sensory pathway, while the latter puts a stop to the excessive contractions of the empty stomach. The sensation of nausea alone appears to traverse the vagi and then only in part, as Walton, Moore, and Graham (1931) found that the vomiting stimuli from peritonitis also run in the splanchnic nerves.

By employing paravertebral injections of procaine, as described by Läwen (1923), von Gaza (1924), and Alvarez (1931), it is possible to

3 of the less successful cases, but in only 1 had there been any further improvement.

Children with the milder neurogenic variety of the disease are very likely to improve on treatment with one or other of the conservative measures just described. In those that fail, it is so doubtful that sympathectomy will bring about any added benefit that this operation has been largely abandoned. For the more advanced cases of the disease, where these conservative measures have failed, colectomy was formerly the only recourse. This operation in sickly, malnourished children carried a high mortality, and the results were not always successful, as proximal dilatation of the ileum often ensued.

For resistant cases of congenital megacolon an entirely new surgical treatment has recently been developed by Swenson, Rheinlander, and Diamond (1949) from the Children's Hospital in Boston. As a result of motility studies of the dilated large bowel with multiple recording balloons, it is their contention that the primary pathology is located not in the dilated hypertrophied colon but in the distal, nondilated rectosigmoid. They observed the progress of active peristaltic waves along the enlarged colon, but these failed to enter the narrow distal segment which exhibited increased tonus. This physiological defect appears to be the cause of chronic partial obstruction. The malfunctioning segment corresponds to the narrow irregular rectosigmoid visualized by X ray in which there is a remarkable absence of ganglion cells in the myenteric plexus on histological examination. At the time of this preliminary report, removal of the narrow irregular rectum and rectosigmoid by a special surgical technique had resulted in what appeared to be 33 complete cures and a single postoperative death. Within three months after operation the appearance of the large intestine had been restored to normal on fluoroscopic examination with barium enema, and it was possible to demonstrate normal colonic peristalsis by balloon studies.

III. Alleviation of Pain from the Abdominal Viscera

The following evidence indicates that the sensory axons from the abdominal viscera run with the sympathetic nerves, primarily in the splanchnics: When these nerves are cut, Sheehan (1932) found that the sensory endings (Pacinian corpuscles) in the mesentery undergo degeneration; when stimulated by means of a bipolar electrode in the course of operation under local anesthesia, severe pain is produced. This is in the upper quadrant of the abdomen on the side stimulated and has the same low threshold and

may increase the risk of complications of an ulcer." In our experience the complications of duodenal ulcer following splanchnicectomy actually have been no more frequent than in an ulcer population of similar age and sex, with the exception of hemorrhage. This has occurred in a few of our ulcer patients who have undergone splanchnicectomy. The bleeding has tended to be severe and persistent, requiring prompt surgical intervention for its control.

As is the case with the stomach, small-bowel pain is transmitted over the splanchnic trunks (Herrin and Meek, 1945). Chronic intractable pain from this source is a clinical rarity except in cases of partial obstruction. When of neurogenic origin, its amenability to splanchnicectomy is illustrated by the following case histories:

Sylvia H., Beth Israel Hospital #24906. This young woman had complained for several years of excruciatingly severe low abdominal pain which came in waves, with severe constipation, increased peristalsis, and vomiting. She had a very redundant colon with irritability and spasm of the cecum and ascending colon. In this state she was unable to tolerate any enemas, as these precipitated an agonizing attack of pain which lasted for hours and required large doses of opiates for relief. For this condition she had been subjected to a series of four laparotomies, but entirely without benefit.

To test the pathways of pain transmission, paravertebral injection of her upper lumbar sympathetic ganglia and splanchnic nerves was carried out by infiltrating procaine at the sides of the first and second lumbar vertebrae. This gave complete relief, so that even a high enema was tolerated without discomfort.

10/10/39: Right-sided splanchnicectomy and resection of the upper lumbar sympathetic ganglia was performed, following which she became free of pain on the right side.

10/23/39: A similar operation was performed on the left side.

Following this bilateral denervation she has had normal bowel movements and experienced no unusual discomfort when her colon was completely filled in the course of a colonmetrogram. The motor function of her colon was normal, and pain relief was complete twenty months after operation.

The cause of pain in the case reported above was at the time obscure, and no explanation could be found on repeated laparotomies. Recent studies by Sarnoff, Arrowood, and Chapman (1948) with differential spinal block (see below) have shown that abnormal peristalsis in the small intestine, with areas of stasis and excessive proximal contractions, may produce this picture of intestinal dyskinesia or neurogenic intestinal obstruction. Commencing typically with removal of a "chronic appendix" for ill-defined abdominal pain, these unfortunate patients are likely to undergo

map the segments which transmit sensation in painful conditions of the gastrointestinal tract (Table II, p. 136). The technique for this will be discussed in detail in Chapter XX.

A. PAIN FROM THE GASTROINTESTINAL TRACT

Pain from the esophagus, at least to a large extent, is not transmitted over the splanchnic nerves or other thoracic sympathetic rami; C. M. Jones and Chapman (1942) have shown that balloon distention is felt after a wide variety of thoracic sympathectomies, after spinal anesthesia carried up to the fifth thoracic segment, after cordotomy with analgesia to the third thoracic segment, and even after transection of the cervical cord. It is probably carried over the vagus nerves. Below the diaphragm, however, the vagi are rarely if ever of clinical importance in the transmission of pain (see above).

In painful conditions of the stomach Läwen (1923) has demonstrated that the sensory pathways enter the spinal cord in the sympathetic rami connected with the seventh and eighth thoracic spinal nerves. Experiments in dogs by Balchum and Weaver (1943) have shown the importance of the splanchnic nerves in afferent innervation of this organ. Aside from gastritis and peptic ulceration, pain arising from the stomach is rare and when present usually signifies carcinomatous extension into the mesenteries and the nerve plexuses in the posterior abdominal wall. Under such circumstances it is questionable whether it can be relieved by splanchnicectomy. We have had no experiences with sympathectomy for intractable pain of gastric origin, but in 2 patients with ulcers in the posterior wall of the duodenum eroding into the pancreas, in whom hypertensive heart disease and angina pectoris contraindicated major surgery, pain was effectively relieved by paravertebral alcohol injection against the sides of the fifth, sixth, and seventh thoracic vertebrae on the right side. This was followed by freedom from pain up to a fatal coronary occlusion eleven months later in the first case, and for over eight months in the second. In ordinary circumstances relief of ulcer pain by splanchnic interruption would seem inadvisable on account of the hazards of painless penetration or an increased tendency to bleed. The likelihood of these complications must, however, be extremely remote. Hightower, Morlock, and Craig (1950) have been over the records of nearly 1,000 splanchnicectomies performed at the Mayo Clinic to determine the statistical chances of such occurrences. They found 21 patients who had proved cases of peptic ulceration either prior to or following sympathectomy. Their records "do not substantiate the view that splanchnicectomy and thoracolumbar sympathetic ganglionectomy

No adhesions were found, but a large and redundant cecum was sutured to the abdominal wall.

1940: A right sacroiliac fusion was performed for the relief of low back pain.

1944–46: Repeated attacks of abdominal pain with vomiting, distention, and obstipation required numerous hospitalizations for tube suction and sedation. In March, 1946, the pain became so severe that another exploration was undertaken, following the observation that barium was held up in the terminal ileum. At this operation no point of obstruction could be found, and it was concluded that the recurring bouts of obstruction must be caused by some form of neurogenic mechanism.

In October, 1946, the patient was again admitted in the course of a severe attack and differential spinal block was tried. There was no loss of motor power, touch, or position sense, but loss of sensitivity to pinprick rose to the eighth thoracic dermatome with vasodilatation and loss of sweating in the lower extremities. Coincident with the sympathetic block, borborygmi and the passage of gas indicated increased intestinal peristalsis. The abdominal distension disappeared with a 4 in. reduction in girth. The patient felt that her attack had been completely relieved. Accordingly, a right transthoracic sympathectomy with splanchnicectomy was performed. In the ensuing eleven months she was able to work again and gained eleven pounds. There was no further right-sided discomfort, but two milder attacks of left-sided pain and distention required a similar left-sided denervation. Since that time she has had no further symptoms.

In contrast to the visceral colic caused by distention and increased peristalsis, pain from cancer of the intestinal tract is not amenable to treatment by intervention on the sympathetic nerves. The discomfort is usually due either to obstruction or to involvement of the somatic nerves in the lumbosacral plexuses. In the former case, in the presence of mechanical obstruction, resection and enterostomy or some type of short-circuiting operation is indicated; in the latter, anterolateral cordotomy is necessary.

B. PAIN FROM THE LIVER AND BILIARY PASSAGES

The anatomy of the biliary innervation has been described in detail by W. F. Alexander (1940) and Womack and Crider (1947). R. M. Moore and Singleton (1933) studied biliary pain in animals by injection of irritant solutions into the hepatic artery. They found that the great majority of afferent fibers pass up the right splanchnic nerve, but that, in addition, a few may be carried in the left splanchnic as well.

In a woman with metastatic carcinoma of the liver following radical mastectomy, the enlarged liver filled the entire right side of the abdomen and caused intense pain throughout this area. The patient happened to be

laparotomy after laparotomy for "postoperative adhesions." They suffer from persistent constipation, with bouts of crampy abdominal pain, distention, and even vomiting. When spinal anesthesia to the upper thoracic level is induced with a dilute (0.2 per cent) solution of procaine and without preliminary morphine or atropine, these individuals develop a vasomotor, sudomotor, and visceromotor paralysis with the blocking of the finely myelinated and unmyelinated sympathetic fibers in the ventral roots. Sensation to pinprick, which is also mediated by the finer axons in the posterior spinal roots, is likewise interrupted, but the larger myelinated fibers which carry sensation of abdominal distention, as well as touch, position sense, and motor impulses to the abdominal muscles, remain intact. Under these circumstances peristaltic activity not only increases but becomes better co-ordinated, and colicky pain is relieved with the passage of large amounts of flatus and feces; the distended rigid abdomen becomes scaphoid, often with a reduction of several inches in girth.

Sarnoff and his associates have shown that this method of differential spinal block may be utilized to distinguish between neurogenic and true intestinal obstruction on a mechanical basis. Under these circumstances the patient is set up for laparotomy, and anesthesia is induced with the continuous spinal needle in place. By waiting for sixty to ninety minutes, obstruction, when of neurogenic origin, will be aborted by passage of gas and feces. Three patients with repeated attacks were effectively relieved by thoracolumbar sympathectomy and splanchnicectomy.

The following case history, taken from Sarnoff's article and the case records of the Massachusetts General Hospital, is a good illustration of the value of these diagnostic and therapeutic procedures. This was the first of a series of patients to be treated by this new method.

A 38-year-old woman was first admitted to the Massachusetts General Hospital in 1933 on account of repeated bouts of cramp-like abdominal pain. These had persisted following an appendectomy in 1923, in which an operative diagnosis of "congenital adhesions" had been made. A previous lysis of adhesions had been performed at another hospital in 1929. From 1933 to 1946 she had repeated bouts of nausea and vomiting with abdominal distention and pain The long, unfortunate saga of surgical interventions to which she was submitted over these thirteen years ran as follows:

1933: A second lysis of adhesions for fecal vomiting with distention, after which an ileostomy was necessary.

1934: Cholecystectomy for cholelithiasis. This operation was followed by a period of mental depression, which required treatment on the psychiatric service.

1935: Re-exploration for recurrent distention with increasing constipation.

in adhesions. After cholecystectomy he was able to pass a probe down the common and cystic ducts into the duodenum.

A year later she was again admitted because of increasingly severe right upper quadrant pain, which had recurred in attacks during the past month. At this time there was a palpable tender liver and a slight elevation in the icteric index and Van den Bergh level of serum bilirubin without obvious jaundice. It was necessary to re-explore the common duct. On probing with a 2-mm dilator, an obstruction was met at the ampulla of Vater. The duodenum was then opened and the stenosed ampulla cut to permit the passage of larger dilators up to the 6-mm size, but none larger than this could be slipped down the narrow common duct. The duct was then drained by a T tube, and the patient was discharged with the tube in place. As long as the bile escaped there was no pain, but it would return on clamping the tube and disappear again with its release.

After a few weeks the tube came out and the sinus closed. Thereupon the old pain soon recurred, so that she was having constant discomfort in the right upper quadrant, and occasional sharp attacks which were different from her old gall-bladder colic. At these times pain radiated into her right scapular region, neck, face, and occasionally down the right arm. There had been no fever, chills, or jaundice. In the absence of evidence of obstruction it was concluded that bile must be reaching the duodenum through the contracted ampulla, but under sufficient back pressure to cause pain from distention of the biliary ducts. In view of the findings at her previous operation, it was evident that the difficulties and risk involved in obtaining a permanent dilatation of the stenosed ampulla would be far greater than an operation to relieve her pain. Evidence obtained from the animal experiments recorded above and from the patient with carcinoma of the liver indicated that resection of the right splanchnic nerves would give the necessary relief.

Accordingly, on 5/2/38 the major and minor splanchnic nerves were resected in addition to a short length of the sympathetic trunk through a posterior supradiaphragmatic approach on the right side. The patient was discharged on the tenth day after operation and has remained free of the long-standing symptoms of increased pressure in the biliary ducts.

We have had occasion to observe the effect of unilateral and bilateral splanchnicectomy upon upper abdominal pain in a group of 12 women with pain of this sort which persisted after repeated laparotomies. The pain was regarded by the patients as the same as that for which cholecystectomy had been performed. In most of the cases exploration of the common duct had been carried out at the original or at subsequent explorations. The majority of the patients originally had gallstones. The common ducts in some were normal and in others appeared to be dilated. In a few the ampulla of Vater appeared to be stenosed. The pain in these cases was severe, requiring morphine for relief, and occurred frequently enough to justify a further attempt to relieve it. Several had become drug

hypersensitive to all opium derivatives, so that no relief was possible through medication. Paravertebral block with alcohol gave most satisfactory relief of pain during the terminal fortnight of her life. Injection in this case was made over the extent of the right splanchnic rami (T6 to T9) and caused very slight discomfort.

Animal experiments (Davis, Pollock, and Stone, 1932) have shown that gall-bladder pain is referred over the right major splanchnic nerve. Zollinger (1933*B*) has shown that distention of the common bile duct in man is a cause of severe pain. Womack and Crider (1947) claim that from 5 to 20 per cent of patients with characteristic symptoms of cholecystitis and with the classic pathological findings at operation will continue to have their symptoms in varying degrees of severity after operation. They believe the presence of scar tissue around the plexus of nerves which surrounds the common and hepatic ducts is the cause of these symptoms. They include in their paper some excellent photomicrographs of nerve fibers compressed in scar, and they reproduce the beautiful dissections, made by Raigorodsky (1928), of the nerve plexuses along the common, cystic, and hepatic ducts. Another valuable anatomical description of the innervation of this region is to be found in the more recent article of Royster *et al.* (1949).

Splanchnicectomy has now been successfully performed on a number of patients suffering from chronic biliary pain which was intractable to direct surgical attack (Craig, 1934) In 4 patients with so-called "biliary dyskinesia," after direct surgical exploration had revealed no cause for pain, Grimson, Hesser, and Kitchin (1947) have resected the right celiac and superior mesenteric ganglia with good results in 3. Pain recurred in the fourth after nine months. Mallet-Guy and Guillet (1943) have reported many successful results from resection of the right splanchnic nerve beneath the diaphragm. It has seemed to us advisable to resect the lower thoracic ganglia and right splanchnic nerves through the posterior paravertebral approach, which gives a far better exposure and permits removal of these structures to an adequate extent to prevent regeneration. This will also interrupt pain from the head of the pancreas, if there are concomitant fibrosis and obstruction of its ducts. This operation was first used in the Massachusetts General Hospital in the following case:

Helen S., 45, MGH U-88059 BM. This patient entered the hospital in 1936 with a long-standing history of gall-bladder attacks. Five years previously her gall bladder had been drained at another hospital, but attacks of right upper quadrant pain and vomiting had continued. There had been no attacks of fever or jaundice. On re-exploration one of us found her gall bladder buried

taken to exclude duodenal ulcer. At one of her several laparotomies a duodenotomy was also done to exclude ulcer. In retrospect the course in this case suggests that the attacks of pain were probably due to recurrent duodenal ulcerations.

This case re-emphasizes the need for excluding all other possible causes of abdominal pain before considering splanchnicectomy. It should be used only as a last resort. The last case has also been a complex problem.

After cholecystectomy with removal of stones from the gall bladder and common duct fifteen years previously, this woman complained of recurrent attacks of severe right upper quadrant pain similar in every respect to those which she had experienced before the operation. Three further laparotomies had been carried out with re-exploration, dilatation and drainage of the common duct at the last two. Cholangiograms were repeatedly negative. Following right-sided splanchnicectomy, the patient was relieved for a year. Then attacks of epigastric and left upper quadrant pain returned with sufficient frequency and severity to necessitate a left supradiaphragmatic splanchnicectomy. The patient was well for a year and a half after this, only to suffer a recurrence of attacks of upper abdominal pain with gradually increasing frequency, in spite of the fact that balloon distention of the duodenum gave no convincing evidence of intact pathways of visceral pain. Finally, in desperation, another laparotomy was done. The common duct was markedly dilated, and the ampulla of Vater was stenosed. A 4-mm dilator was finally passed through it with difficulty. An anastomosis was made between the common duct and the duodenum, leaving a T tube in place, one limb of which passed through the anastomosis into the duodenum. This was not removed for six months. After this the patient was again well for a year, but recently attacks of pain have begun to appear anew. X rays reveal that the anastomosis is patent, since barium enters the common duct readily. However, it does not leave the common duct promptly, indicating that stenosis of the anastomosis is taking place. It is anticipated that a further procedure will be necessary.

These experiences show that splanchnicectomy may be helpful in the management of recurrent pain following surgery of the biliary tract, but they also indicate that it may fail. Splanchnic denervation should, therefore, be used with discretion, and only after detailed study has revealed no other approach to the problem. These are desperate cases, and they should not be denied any operative procedure which offers a reasonable chance for improvement.

C. PAIN FROM PANCREATIC DISEASE

According to Richins (1945), all the sensory fibers to the pancreas run in the sympathetic system, traversing the celiac ganglia and splanchnic

addicts. The attacks of pain were not associated with fever or jaundice and were almost always accompanied by nausea and vomiting. Upper abdominal distention was not infrequently present during attacks. The pain was deep-seated, usually starting in the right upper quadrant or in the epigastrium In a few it seemed to be felt principally in the left upper quadrant. Radiation to the back and to other areas was not infrequent. Detailed studies invariably failed to reveal any satisfactory explanation for the attacks. In most, this included balloon distention of the duodenum. This invariably caused pain which the patients felt was identical to that noted during the attacks. In general, these patients were tense, emotionally unstable, and seemed to have a low pain threshold.

Because the attacks were so severe and since further abdominal surgery seemed to offer little likelihood of relief, splanchnicectomy was carried out in all 12 cases. If the pain was felt principally or entirely on one side, the lower three thoracic ganglia together with the great splanchnic nerve were resected on the side of the pain. This was carried out by a modified Peet operation (as described on p. 420). After such a denervation, pain is no longer felt on balloon distention of the duodenum on the denervated side but is lateralized to the opposite side. The pain threshold is also raised, as indicated by the fact that it requires a much stronger stimulus to produce pain of equal severity over an area of similar size. It is for this reason that a unilateral procedure may occasionally relieve pain which is felt on both sides of the mid-line. More commonly, bilateral denervations are necessary Following this, no pain can be elicited on distention of the duodenum or upper jejunum.

In 3 patients a right-sided splanchnicectomy relieved the attacks, and the patients were followed for seven, five, and four years, respectively; 4 other patients were relieved for one to two years. The follow-up period in these cases is a little short to be certain whether the results were worth while. Of these cases, 3 had right-sided denervations and 1 a bilateral denervation. Three cases have been followed for less than one year.

In one patient the pain, which seemed entirely left-sided, was relieved for about a year following unilateral splanchnicectomy. Then attacks of severe right-sided pain appeared, necessitating a right splanchnicectomy. This patient again did well for a year, after which the pain recurred. Shortly after this she re-entered the hospital with massive upper gastrointestinal bleeding due to a large, posterior-wall penetrating duodenal ulcer, requiring subtotal gastrectomy with resection of the duodenum beyond the ulcer crater. There have been no further attacks of pain in the three years since gastrectomy. Over the years prior to splanchnicectomy this patient had numerous X rays

caused painful radiation to the left epigastrium, which disappeared completely after the nerves were resected on this side.

Experiences with splanchnicectomy in this country have been reported by Rienhoff and Baker (1947), 1 case; * Ray and Console (1949*B*), 5; Connolly and Richards (1950), 2; de Takats *et al.* (1950), 5; Hurwitz and Gurwitz (1950), 6; and Rack and Elkins (1950), 3. An interesting feature of the last report is the fact that vagectomy was tried in 2 cases but had no effect on the disease process or its symptoms, whereas 3 others had complete relief following bilateral sympathetic denervation. These reports are in agreement that excellent results can generally be counted upon following adequate bilateral denervation of the gland. Occasional good results have followed unilateral operation when the pain was entirely one-sided. Usually, however, pain shifts to the other, less involved side, and a second contralateral operation is necessary. To our knowledge there have been a few reported failures following bilateral sympathetic denervation. These may well be due to fibrotic changes that have spread beyond the capsule into the retropancreatic area which is supplied by branches of the intercostal nerves (see below under section on cancer). Experience to date is insufficient to determine just how often this may be the case, but it is certainly best to try the relatively conservative procedure of sympathetic denervation first, reserving the much more radical bilateral cordotomy for the occasional failure.

The variety of sympathectomy which we recommend is a modified form of Peet's one-stage bilateral supradiaphragmatic exposure with resection of the eleventh ribs (see p. 420). The widest possible extent of the major and minor splanchnic trunks should be removed to prevent regeneration, with added resection of the paravertebral chains. The chain on each side should be followed as high as possible, at least to include the ninth ganglion and downward into the substance of the diaphragm to remove the twelfth thoracic ganglion, but we can see no need for pursuing it further. The denervation can be performed bilaterally in about an hour

We have had personal experience with 4 cases. The following case histories illustrate the need for bilateral denervation.

Evelyn D., MGH U-532719. A 20-year-old, exceedingly neurotic woman had suffered right upper abdominal pain with radiation to the back below the scapula for seven years For this she had been hospitalized and operated

* This patient had both vagi sectioned in addition to the resection of the splanchnic nerves and lower thoracic sympathetic ganglia. It is now generally agreed that vagectomy is unnecessary and may lead to disagreeable sequelae.

nerves. When the latter are cut in experimental animals, the Pacinian corpuscles, the most obvious sensory end organs, degenerate. Within the substance of the gland these fibers follow the blood vessels, as is the case in other viscera. Disease within the pancreas often produces intense pain, either by distention of its capsule or by occlusion and back pressure on its ducts.

In chronic relapsing pancreatitis with calculi obstructing the ducts and parenchymal fibrosis, the pain radiates from the epigastrium to the back below the scapulae. It comes in waves and is so severe that the patient is likely to become a neurotic invalid addicted to opiates and often to alcohol as well. When Whipple (1946) first described pancreatic resection for relief of the painful symptoms, Smithwick (see discussion of Whipple's paper) suggested the simpler alternative of sensory denervation and reported a successful case. Unknown in this country at that time, Mallet-Guy (1936) had proposed treatment by left-sided splanchnicectomy and reported results in 10 cases with Jeanjean and Servettaz (1945). In a recent paper with Jaubert de Beaujeu (1950) he has reported his experience in 70 cases. Of 37 of these, followed one to six years, only 6 failed to obtain satisfactory results. Relief from pain was not always immediate, and it is postulated by the surgeons from Lyons that the good results are attributable to a better blood supply and interruption of nervous reflexes that lead to recurrent bouts of subacute pancreatitis. In addition, the authors claimed to have produced evidence of pancreatitis in animals on splanchnic stimulation. However, in his earlier article with Jeanjean and Servettaz, Mallet-Guy (1945) admitted that 5 out of 10 patients with only a unilateral denervation had had residual attacks on the undenervated right side. The origin of these symptoms was attributed to the biliary ducts, innervated primarily by the right splanchnic system.

According to the American authors Ray and Console (1949*B*) and de Takats *et al.* (1950), the effect of denervation is primarily due to the interruption of pain-conducting fibers which pass through the celiac ganglia, the major splanchnic nerves, and lower thoracic sympathetic ganglia and their white rami communicantes to reach the posterior sensory spinal roots. This has always been our opinion, based on clinical experiences in which pain has rarely been relieved by unilateral denervation on either the right or left side. Ray and Console's "Case 1" continued to have pain after a right-sided splanchnicectomy. Spontaneous pain and local tenderness on deep palpation were felt in the left upper quadrant. At exploratory laparotomy direct stimulation of the head and body of the pancreas also

In summary, we believe that sufficient evidence is now at hand to advocate bilateral resection of the lower thoracic sympathetic ganglia and splanchnic nerves at the primary operation. This procedure is capable of removing all the pain-transmitting fibers from the pancreas. Furthermore, it avoids recurrrence of pain on the opposite side with the risk that the patient may become addicted to opiates and refuse further surgery. There has been only a single mortality in all the cases reported, in contrast to 18 per cent of deaths reported by Eliason and Welty (1948) in the attempts at radical pancreatectomy.

Patients submitted to pancreatic denervation in contrast to pancreatectomy may develop late complications owing to progressive pathological changes in the diseased viscus. Our patient with continued nausea, vomiting, and increasing diabetes is a case in point. A second, reported by Ray and Console (1949B), subsequently developed a painless infected pancreatic cyst, which required surgical drainage. Such complications have been remarkably few, and it is quite possible that the chronic disease process itself is favorably influenced by sympathetic denervation, as suggested by Mallet-Guy and Jaubert de Beaujeu (1950).

Severe pain of pancreatic origin is also seen in carcinoma, and a limited number of splanchnicectomies have been attempted for its relief. We know of only a single success of long duration. This case history from the Cushing Veterans Administration Hospital near Boston has been reported to us by Dr. Henry H. Faxon, chief of the surgical service. The patient was a fifty-six-year-old veteran who had a six months' history of upper abdominal pain with radiation to the back, malnutrition, and an epigastric mass. Exploratory laparotomy had revealed inoperable cancer in the head and body of the pancreas. Supradiaphragmatic splanchnicectomy and removal of the ninth to eleventh ganglia on the right side relieved his severe pain on that side, with only a mild residual on the left. Six months after operation he required no opiates and had gained five pounds in weight.

We have attempted this operation in 3 cases, with relapse in 2 after a few weeks and too brief a survival in the third, who died in diabetic coma a fortnight after his discharge from the hospital. Failures of sympathectomy to relieve pain in pancreatic cancer have also been reported by Ray and Console (1949*B*) and de Takats *et al.* (1950). In contrast to pancreatitis, where the disease is generally confined within the glandular capsule, pain in carcinoma usually occurs when the malignant cells invade contiguous structures and compress intercostal nerves in the posterior abdominal wall. Under these circumstances no procedure short of anterolateral cordotomy can interrupt the afferent pathways.

upon many times. An appendectomy in 1939 was followed by exploration for intestinal obstruction in 1941 and cholecystectomy in 1942. At this time an indurated pancreas was first observed. In 1944 she had a gastroenterostomy "for obstruction" and in 1945 an unsuccessful attempt at radical pancreatectomy. She was severely addicted to morphine and to alcohol as well.

On 6/7/46 right paravertebral procaine block (T10 to L2) relieved her pain completely for two hours. Right transthoracic splanchnicectomy and sympathetic ganglionectomy (T6 to T12) was carried out uneventfully with relief of epigastric tenderness as well as pain. She continued to be highly neurotic, resistant to psychiatric help, and left the hospital against advice. When finally heard from two years later, she had had no further right-sided discomfort but was complaining of left-sided pain. This was somewhat less severe than her previous pain on the right but nevertheless a cause of continued incapacity, and such was her emotional instability that she could not make up her mind to a left-sided operation. This case history illustrates most clearly the need for an initial simple bilateral operation at one stage.

Ida F., MGH U-14830. This 62-year-old divorcee had a history of biliary tract disease for thirty years. In 1929 she had a gastroenterostomy at another hospital because of intermittent epigastric pain radiating into the right side of the back. A choledochostomy was done in 1941, and later the same year a partial gastrectomy was done for gastrojejunal ulcer. Epigastric pain recurred in 1945, and it was finally attributed to recurrent pancreatitis in 1947, when she was discovered to have a serum amylase concentration of 150 units (the upper limit of normal being 50). She continued to have repeated bouts of pain with increased amylase activity in spite of dietary treatment and drugs. Her symptoms kept recurring with increasing frequency, and she was readmitted for bilateral splanchnicectomy in December, 1949. She had had five previous admissions to this hospital. A bilateral Peet operation was done in one stage on Dec. 20, 1949. Eight months after operation she was asymptomatic.

Of 2 other cases operated upon at the Massachusetts General Hospital, one was completely relieved of pain following bilateral denervation. Unfortunately, this woman, with advanced destruction of the pancreas, continued to have painless nausea and vomiting with progressively increasing diabetes. In a later attempt to do a radical pancreatectomy at another hospital, the adherent portal vein was torn, and death ensued from uncontrollable hemorrhage. The remaining patient illustrates the dangers of unnecessarily extensive denervation. The operation was carried out through the transthoracic approach, and a left unilateral subtotal thoracic sympathectomy was performed Following this, empyema developed, then lung abscess. By the time these complications subsided the patient was thoroughly addicted to morphine, suffered continued pain from residual intact sensory fibers on the right side, and refused further surgery.

6/11/29: Injection of the ninth, tenth, and eleventh intercostal nerves with procaine in the posterior axillary line, followed by alcohol injection of the tenth. This injection gave freedom from the painful attacks for six months.

5/6/30: Paravertebral injection of T10 with procaine again caused the pain to disappear.

5/8/30: Resection of ninth and tenth thoracic ganglia and a long segment of the major splanchnic nerve (right).

Following this operation the upper abdominal pain disappeared. For a few months she complained of milder attacks in her lower abdomen and groin, which recurred in 1933 for a short period after the death of her daughter in an airplane accident. These were never referred to the upper abdominal segments, where the visceral nerves had been cut. When last heard from six years later she was perfectly well.

Susan P., MGH U-566425. This 61-year-old single woman had been having upper abdominal pain intermittently for at least twenty-six years. For these complaints, at another hospital, she had gastroenterostomy in 1916, cholecystectomy in 1923, and four other operations between 1928 and 1931 for "partial intestinal obstruction." In 1947 she was admitted to the Massachusetts General Hospital for gastrojejunal ulcer, which improved on diet and belladonna, but only temporarily, and six months later a transthoracic vagus resection was done for recurrence of gastrojejunal ulcer. Although the ulcer healed, she continued to have severe abdominal cramp-like pain immediately after eating. The psychiatrists thought they would not be able to help. Roentgenologic examinations showed a well-functioning gastroenterostomy and no organic disease, but gastroscopy did show a moderate degree of hypertrophic gastritis in the upper portion of the stomach The pain was relieved by bilateral splanchnic block, and on 2/21/50 a bilateral splanchnicectomy with resection of the ganglionated trunks from T9 through T12 on both sides was done. Since operation she has remained free of the postprandial pain, but a feeling of fullness does develop after eating. A chronic mild diarrhea persists since vagectomy and is controlled by paregoric and bismuth

D. GASTRIC CRISES OF TABES

The vomiting and lightning pains which accompany tabetic crises cannot be relieved by paralyzing the splanchnic nerves with procaine (personal experience), or by combined thoracolumbar sympathectomy and splanchnicectomy (Grimson, Hesser, and Kitchin, 1947). The same authors also reported 2 tabetics treated by bilateral vagectomy. Neither was relieved, and one subsequently required a gastroenterostomy for gastric retention. Foerster (1927) has reported cutting many posterior roots and both vagi below the diaphragm without relief of pain, also the failure of splanchnicectomy and even of cordotomy in certain instances. But following the excellent articles of Kahn and Barney (1937) and Hyndman and Jarvis (1940), *section of the spinothalamic tracts has justifiably become the procedure of choice for the relief of the lightning pains in tabetic crises.* If the transection of the anterolateral quadrant is carried to a sufficient extent, relief of both pain and vomiting appears to be reasonably certain. In the past eleven years 7 patients with tabetic crises have been subjected to anterolateral cordotomy in this hospital. These will be reported by White and Sweet (1952), who have found that results in 5 were excellent, but in 2 analgesia (complete loss of pain perception) did not remain at a sufficiently high level, with the result that relief was incomplete in one and nil in the other.

E. ABDOMINAL PAIN OF UNKNOWN ORIGIN

Articles by Archibald (1928), Scrimger (1929), and Alvarez (1931) indicate that certain cases of obscure abdominal pain, where even exploratory laparotomy has failed to demonstrate the causative factor, can at times be relieved by dividing the sympathetic visceral nerves. The method of selecting these cases by diagnostic procaine block has been outlined in Chapter VII. This method has led to a number of brilliant results after all other forms of medical therapy and often numerous ill-advised abdominal operations have failed The following are two cases in point:

Phyllis B., 40, PH #24808. This emotionally highstrung woman developed stabbing attacks of right upper quadrant pain immediately after the sudden death of her husband. Her neurological and general examinations revealed no abnormality except a congenital malformation of the intervertebral disk between the ninth and tenth thoracic vertebrae. Removal of her gall bladder by another surgeon had intensified the severity of her attacks, which became frequent and intolerably painful Half-grain doses of morphine alone gave relief, and the patient was becoming addicted to the drug.

(1936) investigations on the same animal with more refined modern neurophysiological methods. After studying motor impulses over the two sets of nerves to the bladder with the Matthews oscillograph, Evans concluded that "it has been impossible to obtain evidence of a satisfying nature that the sympathetic system plays any part in bladder activity."

In a most impressive study on the human bladder, Denny-Brown and Robertson (1933) demonstrated that urination is a reflex act mediated through centers in the sacral cord. Stretch of smooth muscle in the bladder wall sets off a detrusor reflex over the pelvic nerves, with contraction of the viscus and relaxation of its sphincters. Only after the intravesical pressure rises does the internal sphincter open. The external sphincter opens later, but it cannot be opened voluntarily. Its only voluntary power is the ability to contract and stop the flow of urine. This act is effected by somatic motor impulses over the internal pudendal nerve, whereas the afferent and efferent arcs of the detrusor reflex are carried over parasympathetic axons. Muellner (1950) has recently called attention to another somatic motor mechanism which plays an active role in the voluntary control of micturition. This is centered in the voluntary muscles which raise intra-abdominal pressure and constrict or relax the pelvic floor. Fluoroscopic observation of the bladder filled with a radiopaque liquid gives evidence that urination is initiated by a contraction of the diaphragm and abdominal muscles. This results in a downward thrust on the pelvic floor. The rise in intravesical pressure is the signal for the sphincter to relax. On willful interruption of the urinary stream there is a contraction of the levator ani and its pubococcygeus portion, which raises the base of the bladder and permits the sphincter vesicae to close. There is a simultaneous relaxation of detrusor tone to the resting phase.

No evidence has been discovered that the sympathetic presacral fibers play any role beyond constricting blood vessels and contracting the bladder neck to an uncertain extent. Whether there is a definite internal vesical sphincter which actually contracts in response to sympathetic stimuli is still a debated point. Langworthy, Kolb, and Lewis (1940) believe that the responses of the bladder neck to sympathetic stimuli are entirely a sexual mechanism (part of the mechanism of ejaculation) and have nothing to do with micturition. In addition, they have been unable to detect any abnormalities in micturition after removal of the sympathetic nerve supply. We are prepared to accept this evidence and the work of Denny-Brown and Robertson (1933) and to reject the older theory that the sympathetic system favors the storage of urine and inhibits micturition.

The immediate effect of parasympathetic paralysis, as seen in injuries to

CHAPTER XV

Genitourinary Tract

Knowledge of the arrangement of the pelvic visceral plexuses is based on the painstaking dissections of the French anatomists Latarjet and Bonnet (1913), Hovelacque (1927), Elaut (1932), and Delmas and Laux (1933), and of G. A. G. Mitchell (1935*B*, 1938*B*, 1950) in Great Britain. The results of their studies have been summarized in Chapter III (see p. 49). Briefly, from the surgeon's viewpoint, the bladder, prostate, and seminal vesicles receive a mixed sympathetic and parasympathetic innervation through the hypogastric ganglia. These ganglia form a fine plexus of nerves which lies behind the trigone of the bladder. Their parasympathetic component is derived from the second, third, and at times fourth sacral segments over the pelvic autonomic rami (nervi erigentes) (Fig. 20). Their sympathetic fibers come from the lowest thoracic and highest lumbar segments of the cord and descend in the preaortic and presacral plexuses. In the original description by Latarjet and Bonnet the plexus at the aortic bifurcation was called the "presacral nerve." Elaut, however, has shown that it rarely forms a single nerve trunk. In Hovelacque's terminology it is known as the "superior hypogastric plexus." This is a more descriptive name, but the term "presacral nerve" has come into such common usage that it may be used as a synonym, provided it is understood that it refers to a variable plexus formation. Below the sacral promontory the superior hypogastric plexus forms two paired trunks, the hypogastric nerves, which run to the corresponding terminal plexuses. From these, a great number of delicate fibers are distributed to the pelvic viscera.

Physiology of Micturition. The function of the two systems of nerves to the bladder has been studied in both animals and man. An excellent review of the earlier work in this field was published by Fearnsides (1917). At first it was believed that the characteristic antagonistic action of the two divisions of the autonomic nervous system applied to the control of the bladder. Elliott (1907) may have been responsible for this error, as he found that in the cat "the hypogastric nerves facilitate retention of urine by constricting the sphincter and inhibiting the tone of the detrusor urinae." These conclusions drawn from the cat have been disproved by Evans'

lost. Severe paralysis of this sort is seen in tabes and in combined system disease, but rarely after traumatic injury to the cord or cauda equina, unless there is superimposed malnutrition or infection. After uncomplicated transection of the cauda equina, Munro (1936) and F. C. McLellan (1939) have shown that the bladder, which is severely crippled at first, may regain some degree of function after a period of retraining with tidal drainage. In this stage, which is known as the "autonomous bladder" (Fig. 75, B), some degree of nervous control is mediated by intrinsic ganglia in the vesical wall. With the aid of manual compression of the lower abdomen, the bladder can often be made to empty without too great retention of residual urine.

Whereas injury to the spinal reflex centers in the second, third, and fourth sacral segments or their caudal roots results in severe degrees of paralysis, cystometric examinations have shown that lesions in the descending spinal tracts * and brain are followed (after a brief period of "spinal shock") by a permanently hyperirritable bladder which reacts to a small volume of fluid by precipitate urination. These states have been classified as the "reflex" (Fig. 75, C) and "uninhibited" (Fig. 75, D) types of paralyzed bladder. The action of the cerebral cortex is to inhibit reflex micturition (Langworthy and Kolb, 1933), and an inhibitor center appears to be located in the dominant hemisphere close to the leg area (L. G. Lewis, Langworthy, and Dees, 1935). In the baby and in some adult idiots, cerebral voluntary control of micturition (as well as defecation) is not developed. Urine and feces are ejected at irregular intervals in response to the stretch reflex. With the gradual development of cortical function, a cerebral control is established over these spinal reflexes. Its elimination results in increased reflex contractions of the smooth muscle of the bladder and rectum.

The best description of the physiology of micturition is the monograph of Langworthy, Kolb, and Lewis (1940). After consideration of conclusions drawn from their own outstanding investigations and from many other sources, they deny the existence of any antagonistic action between the sympathetic and parasympathetic innervations of the bladder.

Effect of Sympathectomy on the Paralyzed Bladder. Sympathectomy has little if anything to offer for improving the ability of the paralyzed bladder to empty. Jacobson, Braasch, and Love (1944) at the Mayo Clinic were able to report lasting improvement in only a single patient out of a series of 25 submitted to presacral neurectomy. The only condition in which there is evidence to suggest that sympathetic denervation may be of value

* Barrington (1933) has presented experimental evidence that the descending motor fibers to the bladder are located in the dorsal half of the lateral columns (pyramidal tracts).

the sacral segments of the spinal cord, the sacral roots, or their ventral extension as the pelvic nerves (nervi erigentes), is a flaccid paralysis of the bladder. This was first demonstrated by Elliott (1907), who found that destruction of the spinal cord at progressively lower levels did not destroy reflex evacuation of urine until the second, third, and fourth sacral segments were removed. Of these sacral roots the third appears to be the dominant one supplying fibers to the detrusor and sphincter muscles (Heimburger, Freeman, and Wilde, 1948).

The type of emptying seen in the "atonic" (Fig. 75, A) bladder is usually that of overflow distention, and an effective power to evacuate urine is

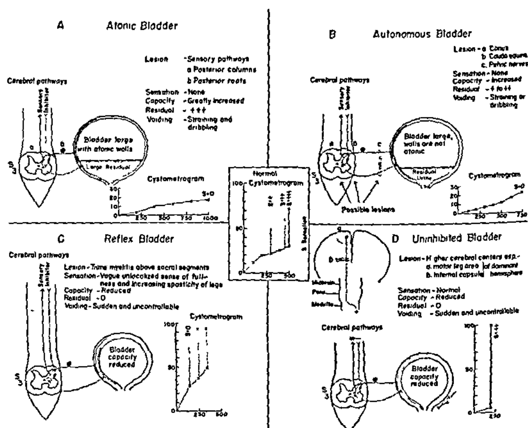


Fig. 75. Classification of different forms of bladder paralysis

This diagram follows the outline given in McLellan's monograph (1939). The distinction between the atonic and autonomous bladder would seem to be one of degree rather than of fundamental difference in the nerve pathways involved. In each the reflex spinal arc is interrupted, and expulsion of urine must depend on the inefficient action of the intrinsic nerve plexuses of the bladder wall and passive compression by increasing intra-abdominal pressure. In the autonomous bladder the paralysis is less severe and atony is less marked (possibly because a few nerve fibers remain intact).

In the cystometrograms given above, the ordinates represent intravesical pressure in centimeters, the abscissas volume of filling in cubic centimeters.

rectal and bladder distention. These latter sensations are carried by more heavily myelinated fibers, which are less easily penetrated by dilute procaine. Pain from bladder inflammation, on the other hand, is abolished by spinothalamic tractotomy.

That the great majority of afferent nerves reach the spinal cord over the parasympathetic trunks is proved by the fact that all painful sensation from the bladder and urethra is lost after section of the posterior sacral roots, injuries of the cauda equina, or the pelvic nerves. Apparently, no painful impulses traverse the sympathetic rami in the superior hypogastric plexus, because no diminution in sensation can be detected after presacral neurectomy, either on distending the bladder in the course of postoperative cystometrograms (Munro, 1937) or on testing its walls with tactile and thermal stimuli in the course of cystoscopy. Although Langworthy, Kolb, and Lewis (1940) believe that the vague sensation of bladder filling which is present in many cases of cauda equina paralysis is transmitted over afferent fibers in the hypogastric nerves, it is highly improbable that any sensation of actual pain is transmitted over this route. This may be mediated, at least in part, by the lowest intercostals, which supply the parietal peritoneum over the fundus of the bladder.

Operations for the Relief of Intractable Bladder Pain. In spite of the evidence cited that the sympathetic nerves play no direct role in the transmission of pain from the bladder, case reports from well-known clinics have recorded relief by means of this operation. Pieri (1926) and Viannay (1927) were among the first to report favorable results of presacral neurectomy in the treatment of painful cystitis. Learmonth (1931*B*) stated that 4 of his 5 cases showed a degree of improvement which left no doubt that the operation was distinctly worth while, although none was completely relieved. Thirteen years later Jacobson, Braasch, and Love (1944) reviewed 37 cases of intractable vesical pain subsequently submitted to presacral neurectomy. Only 3 of these had effective lasting relief, and the authors concluded that "in this respect the operation has been found wanting." In a series of 11 cases, 8 of whom were suffering from tuberculous cystitis, W. J. M. Scott and Schroeder (1938) reported an impressive degree of improvement in 9, considerable improvement in 1, and a single failure after six months of relief. Two of these patients required supplementary intrathecal injection of alcohol, in one to relieve residual burning in the urethra. These surgeons felt that better results could be obtained if the upper sacral sympathetic ganglia were resected with the superior hypogastric plexus. This is contrary to the opinion of Nesbit and McLellan (1939) and most other authorities.

in bladder dysfunction is the rare situation in which dilatation of the bladder and ureters is associated with congenital megacolon (J. P. Ross, 1935; Pässler, 1938). Even this is doubtful, as there have been no recent encouraging reports.

The pharmacological discovery of potent parasympathomimetic drugs, such as the derivatives of acetylcholine and Prostigmine, at first held out hopes that medical therapy might be effective in the treatment of the severely paralyzed bladder. Unfortunately, this has not been the case. In our experience the use of these drugs has been uniformly unsuccessful. Similar conclusions were reached by Nesbit and Gordon (1941), who stated that this form of therapy has "had no clinical beneficial effect in . . . any . . . type of neurogenic bladder." Langworthy, Kolb, and Lewis (1940) do not entirely agree with this, as they have stated that beta-methylacetylcholine hydrochloride is of some value in the treatment of the tabetic bladder. There is, however, a certain risk in the use of any parasympathomimetic drug in the presence of a large urinary residual because of the possibility of vesico-ureteral reflux. Under these circumstances Ney and Horowitz (1950) have recorded complicating acute pyelonephritis.

Third Sacral Rhizotomy for Bladder Retention in Paraplegia. As pointed out above, the third sacral root carries the major supply of parasympathetic fibers to the detrusor and vesical sphincter. Hoen (1945) first proposed bilateral block or section of this root by unroofing its posterior foramen in selected cases of urinary retention. The value of this procedure has been confirmed by Heimburger, Freeman, and Wilde (1948). They advocate preliminary diagnostic sacral foraminal block with procaine followed, if the patient is then able to void, by injection with alcohol or transsacral rhizotomy. A recent description of relief of complete urinary retention after preliminary diagnostic nerve block and subsequent neurectomy of the third and fourth pairs of sacral nerves has been given by Meirowsky *et al.* (1950).

Afferent Innervation of the Bladder. Like all hollow viscera, the bladder is sensitive to overdistention and to spasmodic contraction, which give rise to sensations of discomfort by stretching or squeezing its intramural nervous network. Evidence that this network is excited by the active contraction of bladder smooth muscle against resistance was offered by Simeone and Lampson (1937). These sensations are presumably carried over fairly large myelinated fibers which ascend in the posterior columns, as they are not interrupted by anterolateral cordotomy or differential spinal anesthesia. Sarnoff and Arrowood (1947) have found that dilute procaine blocks sympathetic motor as well as the pain-conducting axons that enter the spinothalamic tract, leaving intact touch and postural sensation, and also that of

no pain and had to get up only once a night to urinate; frequency was reduced to six or seven times during the day.

In contrast to the occasional favorable results in cases of chronic cystitis and irritability of the vesical trigone, little can be expected from resection of the presacral nerves in malignant involvement of the bladder or prostate. One such case (BM #7359), with carcinoma of the bladder developing at the site of an interstitial cystitis, obtained some relief from bladder pain, but no relief from the sense of burning and irritation in the posterior urethra. Rochet (1921) devised a method of resecting the hypogastric ganglia at the base of the bladder and thereby obtained a complete denervation. This procedure was reported by Learmonth (1931*B*) in 2 cases. Although relief can be achieved when the disease has not infiltrated too far into the perivesical spaces, it carries a high rate of mortality and results in complete paralysis of the bladder, which necessitates catheterization. Bilateral section of the spinothalamic tracts (F. C. Grant, 1931), which does not necessarily cripple the bladder, is equally effective and is also an easier and a less dangerous procedure. In the hands of White and Sweet (1952) satisfactory relief of pain has resulted from this operation in all of 14 cases of advanced carcinoma of the bladder and prostate. There was no mortality, and only a single patient developed troublesome urinary retention as a result of the operation. For the distinctly poor risk patient with carcinoma of the bladder and prostate which has not spread into the neighboring tissues (i.e., where the pain is limited to the external genitalia, perineum, and perianal region), White (1938) has advocated a modification of intrathecal alcohol injection. This is carried out with the patient lying in the prone position and the table adjusted so that the lumbosacral spine is flexed and the caudal end of the subarachnoid space is uppermost. A consistent paralysis of the three to four lowest sacral nerves with relief of pain referred to these dermatomes is caused by 1 to 1.2 cc of absolute alcohol injected in this position through a low lumbar interspace. The anal sphincter becomes patulous, but no weakness of the legs has resulted, and impairment of bladder function has not necessarily followed. When patients already have suprapubic drainage or an inlying catheter, this procedure is far superior to resection of the inferior hypogastric ganglia, and it is of outstanding value in certain sufferers who are too sick to tolerate a cordotomy.

Operations for Intractable Ureteral and Kidney Pain. Early studies on ureteral sensation were made by Head (1893), who mapped out areas of referred pain over the two highest lumbar spinal segments. Excellent illustrations of the nerve supply of the upper urinary tract, testis, and epididymis

According to Nesbit and McLellan, it is possible that sympathectomy may relieve certain forms of bladder pain, not by interrupting afferent pathways but by reducing spasm of the internal sphincter. In this interesting paper they describe a series of patients suffering from dysuria secondary to various forms of chronic cystitis with the predominating feature of vesical spasm in whom resection of the superior hypogastric plexus was followed by uniformly good results.

In our restricted experience, sympathetic denervation of the bladder by resection of the superior hypogastric plexus has had a limited value in the treatment of troublesome cystitis. The pain and frequency are usually not entirely relieved, but they may be so reduced that urine can be retained over longer periods in reasonable comfort. This is illustrated by brief case histories of two of the patients who have been submitted to presacral neurectomy.

Mrs. Eva F., 39, BM #1768, was referred by Dr E. L. Young. She had suffered from increasing irritability of the bladder and frequency for ten years. On admission, her bladder had a maximum capacity of 60 cc and she was forced to empty it every half hour because of sharp pain above the pubis. Numerous cystoscopies had shown an extensive area of scarring in the fundus, which cracked open easily. This had been fulgurated on numerous occasions. Urine examinations, including guinea-pig inoculation, had never shown tubercle bacilli.

12/1/30 Resection of the superior hypogastric plexus was performed, from which she made a good convalescence.

Following operation, her bladder capacity remained about the same, but she noticed no more than a dull sense of discomfort above the pubis on distention. She was given a course of cystoscopic dilatations of the bladder by Dr. E. L. Young with further fulgurations of the ulcerated areas. These resulted in still further improvement. Three and a half years later Dr. Young reported that her original degree of improvement had been fully maintained.

Mrs. Jessie McG., 50, MGH U-140453 BM. This patient of Dr. J V. Meigs had interstitial cystitis and a ventral hernia. Following a septic abortion twelve years previously, she began to suffer from dysuria and frequency. She had to get up to empty her bladder three to four times a night and at hourly intervals during the day. Attempts to retain the urine for longer periods caused severe suprapubic pain. Physical examination was not remarkable except for diastasis recti and a large ventral hernia. On cystoscopy, the bladder mucosa was found to be thickened and ulcerated; filling to over 90 cc was intensely painful. The urine contained pus, but repeated tests for tubercle bacilli were negative, and there was no evidence of disease in the ureters and kidneys.

7/22/38: In addition to repairing the ventral hernia and removing the appendix, Dr. Meigs carried out a resection of the superior hypogastric plexus. The result was excellent. When examined seven months after operation she had

paper) have reported lasting relief of renal pain by decapsulation and stripping the nerves from the renal vessels. The most impressive series of renal denervations has been reported by Bauer (1944). In this Swedish series all patients but 1 were freed of intractable nephralgia of unknown origin, 11 for periods of over five years.

We have had a similar experience with 4 patients. In these no explanation for their severe nephralgia could be found by standard urological methods, but the pain was reproducible on distention of the renal pelvis and was temporarily relieved by paravertebral block with procaine along the sides of the upper two lumbar vertebrae. In our later cases at the Massachusetts General Hospital we added splanchnicectomy and resection of thoracolumbar ganglia (T10 to L1) to denervation of the renal pedicle. At the Memorial Hospitals Smithwick has found that removal of the ganglionated chain over these segments alone is sufficient, as this includes the origin of the minor splanchnic and least splanchnic nerves and the major splanchnic does not appear to be concerned with renal pain. In view of what is now known concerning the capacity of the visceral nerves to regenerate, we feel this is of major importance. In a communication from Dr. Peirson he has stated that one of his patients had a recurrence of pain a number of months after operation.

The three following case histories from the Massachusetts General Hospital are given as illustrations:

Mrs. Helen C., 39, MGH U-6814 BM. This patient was referred by Dr. E. L. Peirson, Jr., of Salem, and was treated in collaboration with Dr. S. B. Kelley of the urological service. She complained of dull aching pain in the left kidney region which radiated forward over her lower abdomen. At times this pain became sharp and stabbing, so that she was forced to take to her bed for several days. A year prior to admission to the hospital Dr. Peirson had removed a pair of infected Fallopian tubes, but her pain had not been relieved. On cystoscopy, it was possible to reproduce her pain by overdistention of the left renal pelvis, and X rays taken with opaque media showed spasm of the upper ureter. At the time of her admission to the hospital, deep palpation in the left upper quadrant produced local tenderness.

Paravertebral procaine block of the lowest thoracic and upper lumbar sympathetic ganglia relieved the patient's symptoms for one hour. It was therefore decided to explore the left kidney with the assistance of Dr. Kelley and to denervate the renal pedicle and upper ureter if no local pathology could be found.

These procedures were carried out on 1/5/38. The kidney had a long pedicle so that it was possible to do a thorough exploration. This revealed no gross pathology. The renal artery, veins, and upper 3 cm of ureter were then carefully dissected free of all surrounding nerves, which were resected over a wide

are to be found in G. A. G. Mitchell's (1935*B*) article. Wharton (1932) studied the nerve supply of the ureters in the human fetus by a special clearing and staining technique. His dissections showed that they receive a nerve supply which differs from that of the kidney and bladder. Sympathetic rami run directly to the ureter from the lowest renal ganglia, the lumbar sympathetic chains, and the preaortic plexus. There are further connections between the ureteral nerves and the plexuses that supply the ovaries and testes.

Wharton and Hughson (1931) reported 2 cases of intractable ureteral colic treated by denervation. Hepburn (1934) has reported 3 similar cases, and modified the operation to the extent of freeing the ureter over its entire length through a retroperitoneal incision and then displacing it as far laterally as possible, in order to prevent regeneration of its nerves. These cases had all shown persistent pain in the kidney region, with evidence of irritation and spasm in the ureter on the insertion of a catheter. All occurred in women, and a theory has therefore been advanced that they were caused by reflexes from the closely related genital organs. Pyelography revealed no cause for the attacks other than ureteral spasm. Moreover, Peirson (in discussion of a paper by Stone, 1934) claimed that this pain is relieved by physostigmine, which diminishes ureteral tone, more effectively than by morphine. The results of denervation have been remarkably successful in each case reported. In relieving ureteral pain we prefer to add resection of the thoracolumbar ganglia and splanchnic nerves to periureteral and renal artery denervation, as we believe that this wider neurectomy obviates incomplete denervation and late regeneration of sensory axons.

A detailed anatomical study of the peripheral innervation of the kidney and ureter has been made by Mitchell (1935*B* and 1950). Investigation of the spinal connections in the dog by White and Garrey (unpublished data) showed that pain from distending the renal pelvis can no longer be felt after cutting the last thoracic and first and second lumbar posterior spinal nerve roots. Szabo (1948), who has made an extensive study of renal innervation and reviewed the anatomical literature, claims that sensory and motor fibers arise from the tenth and eleventh thoracic roots as well. It is highly probable that these are the important spinal segments in man, and that motor and sensory impulses reach the renal plexuses over the minor and least splanchnic nerves and the gray rami from the first lumbar ganglia.

Denervation of the kidney causes no obvious change in urinary secretion (see p. 89) but is effective in interrupting pain of renal origin. Hess (1930), E. Stone (1934), Peirson, and Deming (see discussion of Stone's

supradiaphragmatic vagectomies performed in recent years for hypertension and duodenal ulceration. Only temporary adjustments in blood flow and secretion, such as homeostatic adjustments to strong emotion, assumption of the upright posture, etc., are under nervous control.

A possible exception to this statement arises from the recent work of Trueta and associates (1947) in connection with the "renal shunt" phenomenon. After certain forms of renal injury, such as may occur after mismatched transfusions of blood, the "crush syndrome," operative trauma, etc., the Oxford investigators have shown that circulation is diverted from the cortical glomeruli by a short-circuiting of blood in the renal medulla. Trueta claims that this shunt mechanism is mediated by the opening of arteriovenous anastomoses which are under splanchnic control, and that cortical ischemia with resulting anuria may be correctable by interruption of sympathetic discharge. If this is true, procaine block may prove a valuable method for treating reflex anuria, but as yet we have had insufficient experience to form any opinion and know of no convincing published reports.

Relief of Dysmenorrhea and the Pain of Uterine Malignancy. The nerve supply of the uterus differs from that of the bladder, because the greater portion of its visceral afferent nerves run through the superior hypogastric plexus. The nerve fibers in the walls of the uterus are derived from the plexuses of Frankenhaeuser, which are situated in each broad ligament. These are made up of filaments from both the superior and inferior hypogastric plexuses. The ovaries derive their chief nerve supply from the fibers which leave the intermesenteric and renal plexuses and follow the ovarian arteries. In the suspensory ligament the ovarian plexus divides into a number of external branches which surround the Fallopian tube and internal fibers which enter the ovary. The nerves that supply the vagina arise from the anterior part of the hypogastric plexus and from a few sacral root filaments. This brief anatomical description is based on an excellent English review of the work of the French neuroanatomists which has been published by Fontaine and Herrmann (1932) and on the monograph by Reynolds (1939).

It has been the classical teaching that the superior hypogastric plexus exerts a vasoconstrictor effect on the pelvic viscera, while vasodilatation is mediated by the sacral autonomic fibers. However, the exact nervous control of the uterine musculature is still unknown. Resection of the superior hypogastric plexus does not alter the normal menstrual cycle but may precipitate a single atypical period within the first few days after operation. This is probably induced by the intense uterine hyperemia which briefly

area. On discharge a fortnight later, the patient was free of her old pain and remained so during the following eight years.

Frank S., 32, MGH U-168850. This patient was of unusual interest because his fourteen-year history of right flank and groin pain was caused by a single ectopic kidney with its blood supply derived from the iliac vessels. As procaine block from T10 to L2 relieved his pain temporarily, operation was performed on 3/6/44. The twelfth rib was resected and the splanchnic nerves and sympathetic ganglia were removed above and below the diaphragm from T9 through L2 on the right side. He had no further pain in the next two years, and at the end of this period it was possible to distend the renal pelvis without causing any discomfort.

Katherine G., 41, MGH U-295872. Renal pain, which was bilateral, had been relieved on the right by nephropexy, but this operation had been performed without benefit on the left. The patient had left costovertebral discomfort with flank tenderness and intermittent bouts of acute pain. These could be reproduced by distention of the left renal pelvis and relieved by diagnostic procaine block. Thoracolumbar denervation performed on 6/7/48 with resection from the tenth thoracic to the second lumbar ganglia and a greater length of the splanchnic trunks, together with denervation of the renal pedicle, put an end to all her symptoms over the two years and a half in which she has been followed. In addition, no further discomfort could be reproduced on distention of the renal pelvis.

One other patient operated upon at the U.S. Naval Hospital in Chelsea, Mass., was not freed of his symptoms, and it was subsequently discovered that he simulated renal pain to escape service overseas.

Neurogenic Control of Renal Secretion. Early experimental observations of Andler (1925) showed that denervation of the ureter in animals does not disturb its peristalsis nor cause atony, dilatation, or stricture. Frommolt (1928) found that the ureter could be dissected out of its bed from the kidney pelvis to the bladder without impairing the rich anastomotic blood supply which enters it from both ends. Colby (1950), in a recent review, has presented conclusive evidence that rhythmic ureteral peristalsis remains intact after complete external denervation and is initiated by an intrinsic response to urine stretching the smooth muscle fibers of the ureter. None of the drugs in common usage, including morphine, has been found effective in altering ureteral tone or peristalsis. The sympathetic nerve supply carries only vasomotor and sensory fibers.

Evidence has been presented in Chapter IV that the extrinsic nerves to the kidney do not ordinarily control the secretion of urine. No significant changes in urinary output have been observed in the transplanted kidney in experimental animals, nor after the thoracolumbar sympathectomies or

ment is in agreement with a large number of other reports in recent medical journals. The patients must be carefully selected to exclude pain from the ovaries and other related structures, and the resection of the hypogastric plexus must be complete. In performing the operation particular care should be taken to carry the dissection down at least as far as the origin of the internal iliac arteries, in order not to miss the rami from the fourth lumbar ganglia which run under the iliac artery and vein on each side (Fig. 20).

A most instructive report on the value of presacral neurectomy in essential dysmenorrhea has been published by Meigs (1939) from the Massachusetts General Hospital. He is the only surgeon who has given statistics on a series of patients in whom the superior hypogastric plexus has been resected without any other pelvic surgery to becloud the issue. Of his 20 patients, 15 had a successful result. There were partial successes in 2 other cases, and 3 were complete failures. However, in the ordinary patient who fails to respond to nonoperative gynecological measures, Meigs recommended that in addition to the neurectomy the surgeon should routinely dilate the cervix, suspend a retroverted uterus, and correct any other pathological process he may find in the tubes and ovaries. He concluded that this operation is the best form of treatment for patients with true primary dysmenorrhea.

In the nine years after this preliminary report, resection of the superior hypogastric plexus was performed on the Gynecological Service of the Massachusetts General Hospital in more than 100 cases with over 80 per cent good results. Labor in 6 ensuing pregnancies has been painless during the stage of uterine contractions, with only minimal discomfort during the passage of the fetal head through the birth canal. In a recent report Ingersoll and Meigs (1948) have analyzed the causes of failure in 12 cases. They concluded that incomplete sympathectomy explained the poor results in 7, nerve regeneration the late recurrence of pain in 2, and that 3 others had a superimposed psychoneurosis. The latter all experienced pain on anovulatory bleeding (which should be painless) induced by medication with stilbesterol and its subsequent withdrawal.*

Evidence that late return of pain after an early successful result may be brought about by nerve regeneration or by increased conduction of a few fibers missed at operation is given by an experience reported to us by Dr. Joseph H. Phillips of the Free Hospital for Women, Brookline, Mass. Following partial relief for six months after a superior hypogastric neurectomy, dysmenorrhea in this case had again become as bad as ever. Sixteen months

* In this test, 1 mg of diethyl stilbesterol is given for twenty days, starting on the first day of menstruation. Ovulation is thereby prevented. Two to eight days after the drug is stopped, withdrawal bleeding occurs, and the patient should have a painless period. The psychoneurotic woman is likely to complain on sight of blood.

follows pelvic sympathectomy; it should not be regarded as true menstruation. Subsequent periods appear at the usual date after the last preoperative flow. Numerous postoperative observations have shown that pregnancy and parturition are not affected by presacral neurectomy.

The fact that section of the sympathetic genital nerves causes no detectable change in uterine physiology points to the conclusion that they carry mainly visceral sensation. The experimental studies of Leriche and Stricker (1927) give clear-cut evidence of this in animals. Cleland (1933) has shown, both in dogs and in human beings, that uterine pain enters the spinal cord over the eleventh and twelfth thoracic roots. That this applies only to pain from the fundus has been shown by Meigs (1939), who has tested uterine sensation after presacral neurectomy. Taking biopsies from the upper portion of the uterus is then no longer painful, but sacral backache develops when the cervix is dilated, and tubal insufflation still causes discomfort in the right and left lower quadrants of the abdomen. The conclusions to be drawn from these observations are that cervical sensation is transmitted over the sacral nerves, as is pain from the prostate and bladder, whereas sensation from the Fallopian tubes is probably referred over the ovarian pedicles.

The etiological factor in the production of pain during the menses is not known. This subject was discussed by A. A. Davis (1938) in his monograph on dysmenorrhea. He attributed the cause of the pain to the muscular contractions of the uterus, which may be either hormonal (pituitary and ovarian) or neurogenic in origin, and states that "the pain may be due to exaggeration of either motor or sensory impulses by a nerve rendered hypersensitive through inflammation." This fits in well with the observations of Kinsella and others cited on page 369.

In the search for a practical operation for the relief of painful menstruation and carcinoma of the uterus, Jaboulay (1899*A*) first attempted to interrupt the nerves through a perineal incision. Leriche (1925*A*) developed a more successful method by performing periarterial sympathectomy on the internal iliac arteries. This operation gave complete and lasting relief from pain in most cases of dysmenorrhea but has been simplified by Cotte (1925), who advocated the present method of resecting the superior hypogastric plexus. Very gratifying results have been reported after this operation in severe dysmenorrhea. Fontaine and Herrmann (1932) have reported from Professor Leriche's clinic in Strasbourg 22 operations for dysmenorrhea with only 2 failures According to Davis (1938), 75 per cent of the patients with uncomplicated dysmenorrhea are cured by presacral neurectomy, and the majority of the others are greatly relieved. This state-

the three upper lumbar ganglia are resected on one side and two or more of these ganglia on the other. From the over-all statistics it becomes evident that in certain individuals the outflow from L1 and possibly the lowest thoracic ganglia is of major importance in the innervation of the seminal

TABLE XXXIX

Reduction of Sexual Activity following Various Forms of Sympathectomy and Splanchnicectomy

	Permanent Loss of Seminal Emission (Dry Intercourse), Per Cent	*Temporary Reduction to Permanent Loss of Erection (Impotence), Per Cent*
Limited lower thoracic sympathectomy and splanchnicectomy (Peet)	0	0*
Thoracolumbar sympathectomy and splanchnicectomy		
Bilateral resection T7 to T12 on one side, L1 on the other	0	0
Bilateral resection T7 to L1	15	27
Bilateral resection T7 to L1 on one side, L2 on the other	28	16
Bilateral resection T7 to L2	37.5	25
Bilateral thoracic sympathectomy and splanchnicectomy T1 or T2 to T11 or T12	0	57
Bilateral lumbar sympathectomy L2 through L3 or L4	0	0*
Bilateral lumbar sympathectomy L1 through L3 on one side, L1 through L2 or L3 on the other	54	63

* Too few cases are available for establishing accurate conclusions.

vesicles and ducts, while in others the fibers running through the third lumbar ganglion are of equal importance. There is no set rule for this distribution, a fact which corresponds with the well-known irregularities in the arrangement of the lumbar ganglia and the tendency to pre- and postfixation of the spinal sympathetic outflow.

2. Less has been learned from this questionnaire about the reduction in potency, as it was difficult to find out about the exact extent of its impairment or duration. The power of erection appears to be affected as much by the extent of sympathectomy as by the actual ganglia which have been removed. It appears to be damaged most seriously after total or subtotal thoracic sympathectomy and by bilateral removal of the upper lumbar ganglia.

Much has been learned about the anatomical physiology of ejaculation and potency from animal experiments as well as from critical observation in man. The afferent reflex arc for erection on direct stimulation of the penis is via the pudendal nerve to the sacral cord and its efferent arc over the nervi erigentes which dilate the penile vessels (Semans and Langworthy, 1938). Erection on psychical stimulation is mediated by cortico-hypothalamic con-

later the presacral area was again exposed. In cleaning out the connective tissue more radically from the interiliac trigone, Dr. Phillips found "some regenerated nerve fibers and some which I had very likely missed on the first attempt." After this the patient remained satisfactorily relieved of her symptoms.

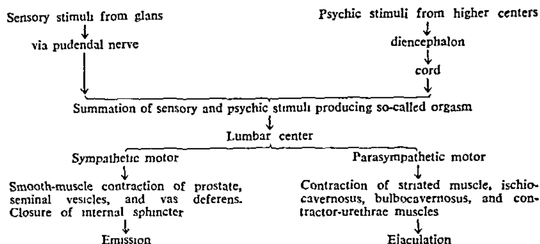
In spite of the fact that a number of papers have advocated resection of the superior hypogastric plexus for pain in malignant disease of the fundus and cervix (Fontaine and Herrmann, 1932; Wetherell, 1933; Greenhill and Schmitz, 1933; Adson and Masson, 1934), we cannot subscribe to this view. In our experience cancer of the uterine cervix and fundus is not painful until the disease has spread out into the paracervical and parametrial tissues Pain is then transmitted over the lower sacral nerves and radiates to the lower back and perineum. On the other hand, when the disease has extended upward along the lymphatic channels and invaded the ovarian pedicles or the lumbosacral plexuses, pain is referred to the groins, buttocks, and legs. In either of these eventualities, cordotomy is the only logical operation

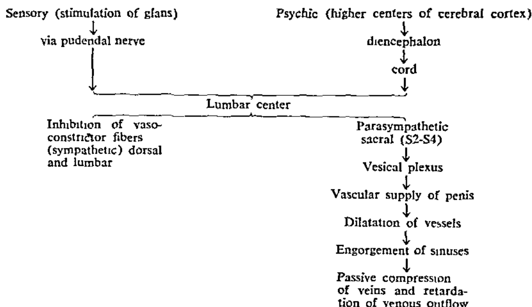
Changes in Sexual Activity following Sympathectomy. While it has been appreciated for many years that loss of seminal emission follows resection of the superior hypogastric plexus, our knowledge has been much less exact concerning the proximal pathways through which these fibers pass and the lumbar ganglia which must be left intact to avoid sterilization of the male. It was also not generally known that extensive sympathectomy may reduce the power of erection and in some cases lead to permanent impotence. The follow-up studies of Whitelaw and Smithwick (1951) on the extensive series of sympathectomies which have been performed at the Massachusetts Memorial Hospitals for hypertension and vasomotor disturbances in the lower extremities have done much to clarify our concepts. From 183 questionnaires returned by patients who have had various forms of sympathectomy, the following facts have become apparent (see Table XXXIX).

1. *Occasionally temporary, but never permanent, loss of ejaculation occurs in men submitted to extensive bilateral thoracic sympathectomy and splanchnicectomy, even though all the lumbar ganglia are left intact.* Absence of seminal discharge is permanent in 15 per cent of cases after thoracolumbar sympathectomy carried down through L1 on both sides, but dry intercourse is not a complication when the first lumbar ganglion has been preserved on one side. When the resection of the sympathetic chains is extended downward to include the two upper lumbar ganglia on both sides, 37 per cent suffer permanent loss. After bilateral lumbar sympathetic ganglionectomy the power of ejaculation is lost in 54 per cent if

feet following sympathectomy of the upper portions of the body, and it may well reduce the degree of erection.

2. "Borrowing-lending" phenomena, discussed by DeBakey *et al.* (1947), may cause a shift of available blood into the sympathectomized areas of the body and prevent necessary shunting into the genital tract.





3. In addition to the above factors, cited by Whitelaw and Smithwick, it would seem that after extensive thoracic sympathectomy reflex increase in cardiac output may also be reduced and play a part, as Whitelaw and Smithwick found that in a few instances even bilateral upper thoracic sym-

nections via a descending pathway in the spinal cord. Erection is therefore entirely a parasympathetic function. The same nerves (second, third, and fourth sacral) likewise activate the spasmodic contractions of the ischiocavernosus and bulbocavernosus muscles at the time of ejaculation. For this reason the sympathectomized male at the time of orgasm does not lose the sensation of ejaculation, even though no sperm is discharged. Other portions of the sexual mechanism are activated by its sympathetic nerves. The propulsion of spermatozoa from the testes to the ejaculatory ducts is dependent on peristaltic activity of ducts to the epididymis and the vasa deferentia. Peristalsis of these ducts and also the contraction of the vesicles are under the control of the pelvic sympathetic fibers (Simeone, 1933). After denervation spermatozoa reach the urethra at a slower rate than normally. Learmonth (1931*A*) has observed seminal emission at operation through the cystoscope on stimulation of the superior hypogastric plexus. Impulses transmitted by these same fibers cause the internal sphincter to close with contraction of the bladder neck, thereby preventing the discharge of spermatozoa into the bladder and directing it into the penile urethra. With the terminal burst of sympathetic impulses the penile vessels constrict, so that the corpora cavernosa contract and erection subsides.

After complete regional sympathetic denervation of the genital tract the sensation of orgasm is not altered, but fewer viable spermatozoa reach the ejaculatory ducts or can be discharged into the prostatic urethra. With the failure of the bladder neck to contract and close the internal sphincter, any emission of semen that may take place tends to back up into the bladder, with the result that little, if any, is propelled through the penile meatus. These reactions have been well illustrated in Whitelaw and Smithwick's diagrams reproduced below:

The mechanism by which potency is reduced or completely lost following a considerable proportion of extensive sympathectomies is less well understood. Erection is temporarily impaired by many major operations, especially in middle-aged men Statistical data derived from Whitelaw and Smithwick's questionnaire are insufficient to give an accurate estimate of the duration or extent of sexual impairment. It is evident, however, that in numerous cases loss of potency is lasting and severe. The following factors appear to be the most likely explanation of partial or complete loss of erection after extensive sympathectomy.

1. After extensive thoracic sympathectomy with the sacral parasympathetic and lumbar pathways, which control erection and ejaculation, all intact, sympathetic vasoconstrictor tone of the penile arteries may become hyperactive. This is the rule with the residual vasoconstrictor fibers to the

PART III

Introduction

In order to produce lasting physiological results, sympathetic denervation of an extremity or viscus must be anatomically complete and carried out in such a way that regeneration cannot take place. In order to prevent regeneration, a considerable length of sympathetic chain or splanchnic nerves must be removed. The powers of regeneration are particularly remarkable in the preganglionic fibers. Gibson (1940), who has made a microscopic study of the sympathetic synapse, has observed degeneration of the boutons (fiber terminations on the nerve cells) in the superior cervical sympathetic ganglion after proximal section of the trunk and their reappearance with the return of function forty-four days later. In the cat, regeneration of preganglionic fibers to the superior cervical ganglion recurs as early as two weeks after interruption (Simeone, 1937). The recent report of Hyndman and Wolkin (1941*A*), suggesting that preganglionic fibers do not regenerate, is not in keeping with our past experience.

In experimental animals division of the cervical sympathetic trunk and transplantation of its two ends to opposite sides of the sternomastoid muscle is followed by regeneration within a month. Lee (1930) has described regenerating axons finding their way through the substance of the muscle. Tower and Richter (1931 and 1932) have shown that cutaneous galvanic reflexes, characteristically abolished when the sympathetic axons are paralyzed, return within a month after cutting the preganglionic rami to the stellate ganglion; but after interrupting postganglionic fibers they observed no return of central activity within a period of eighteen months. These findings are almost identical with the more recent reports of Hinsey, Phillips, and Hare (1939). Haimovici and Hodes (1940) have presented evidence for regeneration even after removal of the entire sympathetic chain on both sides. Simmons and Sheehan (1939), Smithwick (1940*C*), and, more recently, Felder *et al.* (1949) have reported many instances of recurrent sweating and vasomotor activity even after cervicothoracic ganglionectomy with removal of the inferior cervical, first, and second thoracic ganglia.

How preganglionic fibers can bridge the gap left by the removal of the cell bodies of the postganglionic neurons is difficult to understand, and no

pathectomies sufficiently extensive to denervate the heart have resulted in reduction of potency.

4. Whitelaw and Smithwick's assumption that sensitization to adrenaline of the arteriolar smooth muscle of the genital tract which has been deprived of its sympathetic innervation plays an important role following lumbar sympathectomy seems an unlikely factor to White and Simeone. According to Cannon's theories of homeostasis, adrenal medullary secretion is inhibited during conditions when parasympathetic activity predominates. Furthermore, after thoracolumbar sympathectomy the adrenal medullae are denervated, although this is not the case after a sympathectomy limited to the lumbar ganglia. While the nonspecific general and metabolic effects of major surgery (Simeone and Vavoudes, 1948), i.e., the "alarm reaction," may well account for a temporary reduction in potency, it is difficult to explain prolonged disturbances in erection after lumbar sympathectomy on this basis.

In the female, as Fowler and de Takats (1949) stated, "sympathectomy has no adverse effect on the . . . genital tract since many records are available of women who, contrary to our advice, have become pregnant and have borne normal children." Newell and Smithwick (1947) record a high percentage of young wives who, because of high blood pressure, had been unable to bear a living child and who were able to complete pregnancy successfully after sympathectomy. Only 2 of 20 women questioned by Whitelaw and Smithwick reported any change in desire or frequency of intercourse, and an equally small minority noted a reduction in sensory response.

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How preganglionic fibers can bridge the gap left by the removal of the cell bodies of the postganglionic neurons is difficult to understand, and no

histological explanation has yet been given, but if delicate tests are used to demonstrate recovery, such as rise in surface temperature on diagnostic procaine block and fluctuations in electrical skin resistance, a greater or lesser degree of regeneration can be demonstrated in a surprising proportion of patients. The practical importance of this is brought out in Chapter VIII, where a high rate of recurrence of both vasomotor and sudomotor activity has been clearly demonstrated after every variety of peripheral sympathectomy. We have now clear-cut evidence of both motor and sensory recovery after visceral denervation as well.

According to Sheehan (1941) it is conceivable, though unlikely, that preganglionic fibers could extend down into the arm and take over the functions of the postganglionic neurons. It seems physiologically impossible to us that preganglionic axons, which on discharge produce acetylcholine at *their endings, could activate the receptor endings on smooth muscle,* which normally respond to sympathin. In the case of the cholinergic sweat glands this is theoretically possible, but return of sudomotor activity has never been troublesome. Foerster (1935) has suggested that the middle cervical ganglion may be a source of postganglionic neurons to the upper extremity, and such fibers would remain intact after the ordinary cervicothoracic operation. Another explanation has been offered by W. K. Livingston (1939) that, in man, a considerable number of postganglionic cells related to the arm lie in ganglia below the second thoracic; the operation would then merely interrupt their axons and regeneration could be readily effected. Hinsey, Geohegan, and Aidar (1942) have suggested that after sympathectomy a few remaining intact fibers may take on an increasingly important role. In this way it is possible that a few vasomotor and sudomotor fibers in the first thoracic root, whose presence has long been claimed by Kuntz (1949), may establish synapses with postganglionic cells above the level of resection. If this were the case, however, one would expect evidence of recurrent sympathetic activity after a few weeks rather than after a latent period of some nine months, which has usually been observed.

Another likely possibility is that the accessory ganglia, described by Wrete (1943) and Skoog (1947), have rami communicantes which never enter the paravertebral ganglia (see p. 31). The existence of these ganglia, incorporated in the spinal nerves and quite independent of the sympathetic trunk, has been proved in anatomical dissections, at least in the first and second thoracic and the two upper lumbar segments in some human bodies (Kuntz, 1949). The occurrence of such pathways in other spinal nerves is not precluded. These account for the fact that some degree of residual sweating is always present over the anterior thigh after the most extensive

resections of the thoracolumbar ganglia (Ray and Console, 1948). In a more recent article the same authors (1949*A*) have reported return of peripheral sympathetic activity after total removal of both paravertebral chains over the entire extent of the thoracolumbar sympathetic outflow (stellate ganglion to third lumbar inclusive) in 30 patients. At first vasoconstriction and sweating were paralyzed and electrical resistance was elevated over the entire body, but in a matter of days or weeks, long before nerve regeneration could occur, every subject developed recognizable signs of sympathetic activity. These occur in certain characteristic areas, particularly over the thighs and lower abdomen, in response to "the inherent necessity for the body to utilize whatever compensatory mechanisms remain." With the passage of several years there is some return of function over large areas of the trunk, anterior thighs, and arms.* Ray and Console ascribe this return of function whereby homeostasis is preserved within the limits of extreme demands on the body entirely to the existence and augmented activity of sympathetic nerves that are not interrupted by the operation.

Although these mechanisms may play an important part, the fact that secondary operations with removal of paravertebral scar and more extensive ganglionectomy have again abolished vasconstriction and sudomotor activity in the arms in our cases of recurrent Raynaud's disease has forced us to the conclusion that regeneration is the primary cause of late failures. We realize that this is contrary to the opinion of other writers. Papez, Jensen, and Dukes (1945), for example, have studied this possibility by post-mortem examination of dogs two years after removal of the thoracolumbar portion of the sympathetic chains and splanchnicectomy. They concluded that regeneration is small and that the pseudoregenerated trunks contain few functioning fibers. On the other hand Kirgis and Ohler (1944), who investigated this problem in cats, were able to find regenerating fibers bridging the operative gap within a period of four months. As direct evidence for regeneration in man we cite the case of a woman (Dorothy H., MGH U-330565) in whom too short a length of major splanchnic nerve had been resected by one of our surgical residents for relief of intestinal pain persisting after multiple laparotomies. After a six-months' period of complete relief her pain had recurred. When explored again by one of us the major splanchnic had bridged the gap so completely that the only certain proof of its previous interruption was the presence of a dural clip in the upper pole of the celiac ganglion. One of us (R. H. S.) has witnessed

* A striking series of photographs illustrating the progressive return of sweating over a thirty-nine months' period can be found in Fig. 15 of Schafer's article (1945).

similarly complete reconstitution of previously resected short lengths of the major splanchnic nerve on several other occasions.

We believe that one cannot escape the conviction that a sufficient number of pre- and postganglionic motor axons and also viscerosensory fibers regenerate to account for the frequent partial return of vasomotor disorders and, much more rarely, of visceral pain. The problem of how to produce a lasting denervation of the upper extremity has indeed been a difficult one.

The physiological importance of performing sympathetic denervation by interrupting the upper or premotor neuron in order to prevent an exaggerated compensatory response of smooth muscle to adrenine was greatly overestimated in our previous edition. This was due to the fact that we made the mistake of overgeneralizing specific findings in animal experiments. These observations made in rabbits and monkeys by White *et al.* (1936) were in perfect agreement with the well-known previous findings of Cannon and Rosenblueth (summarized 1949). It is now established that human sensitivity to chemical mediators after both pre- and postganglionic sympathectomy does occur, but its importance is overshadowed by the far more important problem, clinically, of regeneration of nerve fibers (Simeone and Felder, 1951; Felder *et al.*, 1949). We have no evidence that preganglionic denervation gives clinical results superior to ganglionectomy. Indeed, other things being equal, regeneration may occur more easily after preganglionic than after postganglionic sympathectomy.

The effective degree of vasodilatation which follows complete sympathetic denervation is most clearly brought out by quantitative measurements. Horton and Craig (1930) and Reichert (1933) have demonstrated the increased arterial caliber by arteriograms. G. E. Brown and Adson (1929) state that whereas the normal ratio of arterial wall to lumen is 1 to 2, after ganglionectomy it becomes 1 to 3.5. Heat elimination, measured by Brown (1926*B*) in the extremities with the Stewart-Kegerreis calorimeter, is increased approximately 70 per cent. Herrick, Essex, and Baldes (1932) have determined blood flow in the legs of dogs by means of the Rein thermostromuhr; this very accurate method shows an average increase of 100 per cent in the denervated extremity tested at nineteen to thirty-four months after operation. Wagener (1931), by means of a special ophthalmoscope, has measured the dilatation of the retinal vessels after cervicothoracic ganglionectomy. In 36 cases of normal vessels he noted vasodilatation in all but one instance (a case of Buerger's disease), and found it still present at the end of a year. In our own cases we have observed elevation in surface temperature amounting to as much as 15°F five years after lumbar ganglionectomy.

No one today can question the effectiveness of resecting sympathetic ganglia or the abdominal and pelvic splanchnic nerves for the relief of visceral pain. It is now generally recognized that pain from the heart and all the abdominal viscera can be interrupted effectively in this way. So long as the disease is confined to the viscus itself and has not spread to involve the parietal peritoneum or somatic spinal nerves, this method of dealing with it is generally superior to posterior rhizotomy or anterolateral cordotomy. In fact, where diagnostic procaine block has been followed by clear-cut interruption of symptoms, the results of sympathectomy are more consistently favorable than the standard neurosurgical procedures that have long been used in the treatment of somatic neuralgias.

A final consideration of importance to the surgeon, especially when he embarks on a secondary sympathectomy after regeneration, is the possibility of subjecting the patient to a severe postoperative neuralgia. Everyone who has had any experience with operations for hypertension, especially with the transthoracic or thoracolumbar approach, has been concerned over complaints of girdle pain and backache which may persist for months. Occasionally, after upper thoracic sympathectomies as well, patients complain bitterly of neuralgia in the shoulder and upper back. Usually, these subside with time, but we have had two women in whom the neuralgia, after multiple attempts to secure lasting release of vasoconstrictor tone in Raynaud's disease, spread from breast to occiput with such severity and persistence as to threaten permanent invalidism with morphine addiction. The first successful section of the spinothalamic tract in the medulla, performed by White (1941), resulted in a satisfactory rehabilitation of the first of these two patients. In the second it became necessary to carry out bilateral transections of the anterolateral columns at the highest cervical levels. This patient also is fortunately relieved. We know of no way to avoid such rare but appalling postoperative complications.

With the awakened interest of clinicians and surgeons in the autonomic nervous system, this branch of neurosurgery is beginning to emerge from its early phase of trial and error. Seventeen years ago, at the time this monograph made its first appearance, knowledge of the anatomy and physiology of the human autonomic nervous system was uncertain, clinical reports were uncritical, and prolonged follow-up statistics were meager. Modern diagnostic tests, accumulation of more reliable case reports, and a better knowledge of the type of operation required to produce a desired physiological effect are the factors responsible for progress. The first two subjects have been taken up in Parts I and II; the discussion of operative technique remains for the final section.

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CHAPTER XVI

Cervical Sympathectomies

Resection of Superior Cervical Sympathetic Ganglion. In order to obtain a good exposure for this operation, the patient should be placed on the operating table with his head rotated toward the opposite shoulder and the neck extended backward over a narrow pillow or bar (Fig. 76). Regional

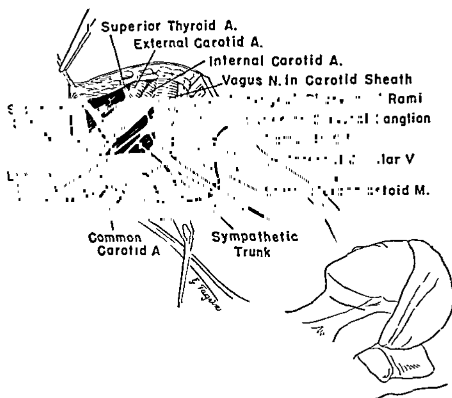


Fig. 76. Superior cervical ganglionectomy.

anesthesia is most satisfactory. It is induced by a subfascial injection of 1 per cent procaine along the posterior border of the sternocleidomastoid muscle. This infiltrates the superficial branches of the cervical nerves and is usually sufficient, although at times it must be supplemented by a further injection around the carotid sheath. Recently, we have used an oblique incision made in a natural crease of the skin a finger's breadth below the angle of the jaw. This should start over the sternomastoid muscle and be

In preparing this section on the technical methods of sympathectomy, vagectomy, and chemical block, we have described the standard procedures in current use at the Massachusetts General and Memorial Hospitals. Previous descriptions have been published in medical periodicals referred to in the text, by White in Bancroft and Pilcher's volume on *Surgical Treatment of the Nervous System* (1946) and by Smithwick in Cole's *Operative Technic in Specialty Surgery* (1949). A description devoted to viscerosensory denervation by White and Sweet (1952) is to be published shortly by Charles C Thomas. The reader who wishes a complete description of alternative methods, especially those in use in European clinics, is referred to the excellent monograph of Lambret, Razemon, and Decoulx (1948) and Tosatti's (1947) small book on the technique of sympathetic infiltration.

incision, while the floor is formed by the anterior scalene muscle (Fig. 78). After the jugular vein and phrenic nerve have been retracted toward the mid-line, the muscle is cut across just above its insertion in the first rib, care being taken not to injure the underlying subclavian artery.*

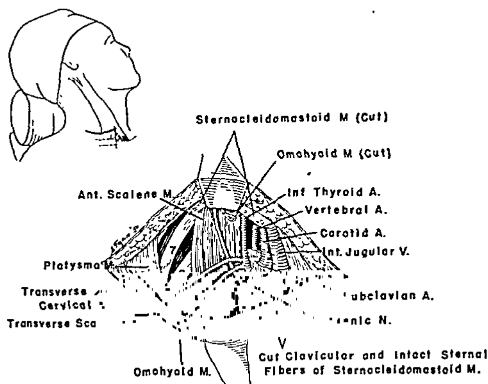


Fig. 77. Cervicothoracic ganglionectomy by the cervical approach. 1. Exposure of the vascular structures and the anterior scalene muscle.

This is the key to obtaining a sufficiently deep exposure to ensure the resection of the upper three thoracic ganglia In addition it gives a clear view of the proximal portion of the subclavian artery, the origin of its thyroid axis and vertebral branches, as well as the lower end of the common carotid (a branch of the subclavian on the right and a separate trunk on the left). After ligation and section of the thyroid axis, the central end of the subclavian is next thoroughly freed by blunt dissection in order to obtain a clear view of the tissues behind the origin of the vertebral artery. The stellate ganglion lies just at this point adherent to the lateral surface of the seventh cervical and first thoracic vertebrae (Fig. 9).

In a left-sided incision the thoracic duct should be identified and retracted out of the field with a thin ribbon retractor. The duct runs forward out of the depths of the mediastinum from behind the jugular vein and

* The subclavian vein lies behind the clavicle and is not usually encountered.

carried forward and downward in the natural cleavage plane of the skin nearly to the mid-line. A 5-cm incision made in this fashion will result in a minimal scar and gives just as good exposure as one made directly over the carotid artery. The incision is carried through the platysma and superficial cervical fascia; its edges are then separated by a self-retaining retractor. The sternomastoid muscle is next retracted laterally, and the carotid sheath is freed. The jugular vein is retracted laterally away from the carotid artery. This exposes the vagus nerve, which runs in the vascular sheath behind the carotid artery and adherent thereto. After these latter structures have been retracted laterally, the cervical sympathetic trunk can be found lying just posteriorly on the longus capitis and longus colli muscles

Once the sympathetic trunk has been found, it should be elevated from its bed and the dissection carried upward. The superior cervical ganglion is a fusiform structure about 3 cm in length, the upper pole of which runs almost to the base of the skull. It must be dissected out by careful blunt dissection, the superior cardiac nerve being cut, as well as the numerous gray rami which connect it with the upper three cervical nerves, the carotid plexus, and the closely associated glossopharyngeal, hypoglossal, and vagus nerves. As these connections are successively cut, the entire length of the ganglion can be drawn into view, until it is possible to cut the rami at its upper pole without risk to other important structures which lie in the immediate vicinity.

We have recently utilized this operation in facial paralysis, to produce a drooping of the upper eyelid and thereby enable the patient to close his eye This is a really valuable procedure (see p. 251).

Stellate Ganglionectomy. Jonnesco (1923), Brüning (1923*B*), Royle (1932*A*), Gask (1933), and Leriche and Fontaine (1933*A*) have been the leading advocates of the cervical approach for stellate ganglionectomy. Resection of the stellate by this route is carried out with the patient in the same position as for resection of the superior cervical ganglion. Intratracheal ether-oxygen insufflation is the safest anesthetic, as by this means the risks of pneumothorax in case the pleura is opened are eliminated.

The most satisfactory exposure is that described by Royle (1932*A*) and further developed by Gask (1933). A transverse incision is made a finger's breadth above the clavicle and carried laterally 5 cm from the sternal tendinous head of the sternocleidomastoid muscle (Fig. 77). The thin clavicular head of the muscle is divided (and later resutured). This centers the incision over the vertebral artery. The omohyoid muscle, which runs obliquely across the field, is cut across and the deep cervical fascia is opened. The jugular vein and carotid sheath lie on the medial side of the

Vieussens, connecting the inferior cervical with the small intermediate and middle cervical ganglia above. These star-shaped rami have given it the name of stellate ganglion and make its identification an easy matter. When this structure has been freed from its bed, the chain can be followed down as far as the third thoracic or even a lower ganglion with very little difficulty. Care should, however, be taken not to injure the contiguous highest intercostal artery, which is a branch of the costocervical trunk of the subclavian.

Once this upper portion of the sympathetic chain has been exposed, the best method of dealing with it depends on the purpose to be accomplished. In angina pectoris a maximal length of trunk should be resected in order to interrupt all the lower direct cardiac nerves, which arise from the third and possibly the fourth thoracic ganglia. We therefore recommend its resection from the stellate ganglion down to include the fourth thoracic. In Raynaud's disease, since the uppermost preganglionic fibers enter the second thoracic ganglion, Telford (1935) recommended cutting the sympathetic trunk below this level and swinging the decentralized cephalic end up into the cervical muscles in order to prevent fibers from bridging the gap between the two divided ends of the chain. After completion of these procedures and after all bleeding points have been dealt with, the incision is closed in layers without drainage. The clavicular head of the sternocleidomastoid muscle is resutured, but the separated ends of the scalenus anticus cannot and need not be approximated.

Although this supraclavicular procedure has been favored by Olivecrona for sensory denervation of the heart (see p. 264), it is difficult to make certain that all the lower connections at the level of the third and fourth ribs have been interrupted. For this reason we have concluded that the posterior approach is best. In our opinion this is also the case in Raynaud's disease. While Telford (1935) has shown that it is possible to do a preganglionic denervation of the upper extremity by dividing the chain below the third thoracic ganglion, cutting the communicant rami of T2 and T3, and transplanting the cephalic stump into the deep structures of the neck, we believe that this is followed by a very high incidence of recurrence. We therefore prefer to resect in addition the roots of the second and third intercostal nerves within the dura, a maneuver which necessitates the posterior approach (see below). In hyperhidrosis, where resection of the second and third thoracic ganglia is sufficient to ensure permanent relative dryness of the hands, this procedure can still be used. Nevertheless, we do not recommend it, as we consider it somewhat more difficult and more likely to result in complications than the posterior approach.

enters the subclavian just lateral to its junction with the jugular. This stage of the operation requires a bloodless field and the best available illumination from either a lighted retractor or a headlight. Needless to state, considerable care must be taken not to puncture the apex of the pleura nor to injure the thoracic duct or one of the large blood vessels. In order to expose the sympathetic chain as low as its third or fourth thoracic ganglion, which is about the maximum extent of trunk which can be resected by this approach, the surgeon should next cut Sibson's fascia, which attaches the apex of the pleura to the posterior portion of the first rib. When this step has been carried out the entire apical pleura can be readily freed by blunt dissection. It is then a simple matter to visualize the inferior cervical and first thoracic ganglia (Fig. 78). This double ganglion is usually a dumbbell-

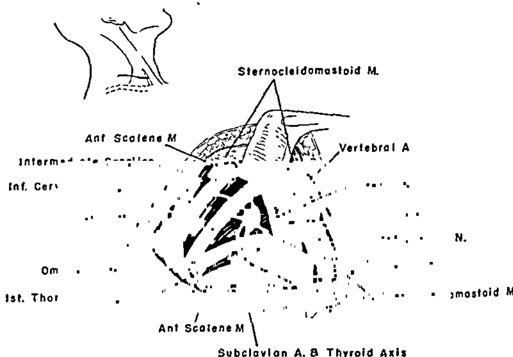


Fig. 78. Cervicothoracic ganglionectomy by the cervical approach
2. The scalenus anticus muscle has been divided and the subclavian vessels and dome of the pleura retracted downward The retraction of these structures has been purposely exaggerated in order to show the first thoracic ganglion.

shaped structure, 1.5 to 2.5 cm in length, made up of the two ganglia connected by a distinct isthmus, although at times both portions are fused into a single mass. Its lower portion lies immediately in front of the first thoracic nerve and against the head of the first rib. Its upper pole ends in a number of fine rami which connect it with the lower trunks of the brachial plexus. Others surround the vertebral artery and the subclavian by the annulus of

the first will be identified with certainty. An X ray is essential to exclude a cervical rib. When the third rib has been identified, the overlapping edge of the iliocostalis and longissimus cervicis muscle is divided to expose the articulation of the rib and transverse process. The intercostal muscles are then separated by sharp (scissors) dissection from the upper and lower borders of the rib, and the inner 4 to 5 cm are removed, including the periosteum. If one divides the external intercostal muscle and the fascia between it and the internal muscle layer close to the rib, one can then pass a finger around the rib, outside of the periosteum but between it and the pleura. The intercostal nerve, artery, and vein, separated with the muscle, should not be injured. This technique is preferable to subperiosteal resections in this region. The tip of the transverse process can be removed with rongeurs, and the underlying remnant of rib is removed for 2 cm or so.

The next step is to separate the pleura with a finger to the mid-line of the vertebral column, to a point above the second and below the fourth rib, and laterally to the resected rib end. The fourth rib is then resected in a similar manner. The third intercostal bundle with the exception of the nerve is then removed. The third intercostal nerve is readily visible in the middle portion of the wound, the second being concealed beneath the second rib in the upper portion of the wound, while the fourth intercostal nerve is seen crossing the lower portion of the wound (Fig. 79, a). The following maneuver, depicted diagrammatically in Figure 79, c, is then carried out. It is called intraspinal root section and is designed to prevent regeneration from the second, third, and fourth thoracic segments. When the third intercostal nerve is picked up with a hook, make certain that the intercostal artery and vein are not included. The nerve is divided at the lateral extent of the incision. It is followed to the intervertebral foramen, dividing the communicating rami running from the anterior aspect of the nerve to the corresponding thoracic ganglion. A dental spatula can then be slipped about the dorsal branch of the intercostal nerve, and this is divided. This branch runs vertically and posteriorly between the transverse processes and is given off just lateral to the posterior root ganglion. The latter then comes into view, and the spatula is inserted between the anterior and posterior roots at the proximal end of the ganglion. The posterior root is divided with a knife against the spatula blade, leaving the anterior root intact. The arachnoid is then pushed medially with the spatula and separated from the anterior root, so that the latter is white and glistening and is free in the foramen. A small spinal-fluid leak results. The root is then divided with scissors, so that its lateral centimeter is removed. The proximal

CHAPTER XVII

Thoracic Sympathectomies

I. Denervation of the Upper Extremity

The major consideration which influences the choice of surgical technique for denervation of the upper extremity is the prevention of regeneration. It is of importance also that the denervation be complete. A denervation which is largely preganglionic in nature is thought by some to be preferable to one which is largely postganglionic in nature (Telford, 1935; Smithwick, 1936). It has so far been impossible to accomplish all of these aims to our complete satisfaction. These matters have been discussed in detail in Chapter VIII, together with an evaluation of the clinical results of various techniques.

Posterior Extrapleural Approach. This approach is preferred by the authors to the anterior cervical or transthoracic routes. One can perform either a so-called "preganglionic sympathectomy" or a ganglionectomy or a combined maneuver by this exposure of the cervicothoracic chain. The patient is placed in the prone position with firm pillows beneath the upper thorax and pelvis so that there is no compression of the abdomen. The arms are placed at the sides, there being sufficient support under the sternum so that the shoulders droop forward. This carries the medial border of the scapulae away from the mid-line. Intratracheal anesthesia should be used.

A paravertebral incision about 7 cm long is made and centered opposite the space between the second and third thoracic spinous processes. It is placed 4 cm lateral to the mid-line. After careful application of skin towels, the incision is carried down through the deep fascia to the trapezius muscle. The fibers of the latter are incised vertically for several centimeters in the center of the incision This exposes the underlying rhomboid, which is divided obliquely in the direction of its fibers. A finger can then be passed upward and downward beneath this muscle and the ribs palpated and counted accurately. If the incision is properly placed, the oblique split in the rhomboid will lie directly over the third rib. The first rib is sometimes a little difficult to feel. The second is very prominent, and beginners are apt to count it as the first. If one feels carefully over this prominent rib

nerve hook between the second and third ganglia (Fig. 79, a). The second, third, and fourth sets of communicating rami are clipped and divided. The trunk is clipped and divided just below its fourth ganglion. The latter is cut away, and the decentralized second and third ganglia are encased in a silk cylinder. The distal stump is then sutured to the intercostal muscle in the upper portion of the incision (Fig. 79, b).

The incision is closed carefully in layers with interrupted silk sutures, a catheter (No. 24F) having been placed in the extrapleural space. After the wound is closed, any residual air is aspirated, and the catheter is removed. If the pleura is opened, no attempt is made to close it. Instead, a second catheter is inserted within the pleural space and aspirated after the wound is closed, while gentle positive pressure is used to expand the lung. The catheter is then withdrawn. The late results of this operation are superior to those following various other techniques which we have tried. It has not, however, eliminated the problem of regeneration. As an alternate technique the principle of intraspinal anterior root section can be combined with cervicothoracic ganglionectomy. This should eliminate the small percentage of denervations which are originally incomplete. It should not, however, prevent regeneration or influence the late results any more than does cervicothoracic ganglionectomy (postganglionic sympathectomy) alone. We favor denervation of the upper extremity as described as the best primary maneuver, to be followed later by cervicothoracic ganglionectomy by the anterior approach if regeneration of consequence occurs

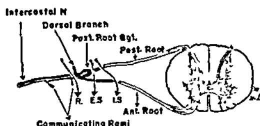


Fig. 80. Various methods of interrupting sympathetic outflow from the second and third thoracic segments.

In technique R., the point of proximal section of the second and third intercostal nerves is lateral to the posterior root ganglion. In E.S., the anterior and posterior roots are divided separately at a point just medial to the posterior root ganglion. In I.S., the posterior root is sectioned as in E.S., but the anterior root is divided more medially within the arachnoid. In all instances the rami communicantes are divided, and a 5-cm segment of the second and third intercostal nerves is removed (From Smithwick, R. H "The rationale and technic of sympathectomy for the relief of vascular spasm of the extremities." *New Engl. J. Med.*, 1940, **222**: 699–703, courtesy of Massachusetts Medical Society, Boston)

When either pre- or postganglionic sympathectomy is done for hyperhidrosis, late recurrence of sweating has not been a problem. This has never been excessive, and the slight reinnervation of sweat glands which may ultimately take place is actually an advantage, as it merely prevents

end retracts within the canal and, after the meninges heal, theoretically it should not regenerate. This method of sectioning the nerve roots (I.S) is illustrated diagrammatically by Figure 80, which also shows previous techniques, extraspinal root section (E.S.), and ramisectomy (R). These do not appear to be so effective in safeguarding against regeneration. The second and fourth intercostal nerves are treated in a similar fashion.

After the rhizotomy has been completed, the sympathetic trunk is palpated. It lies on the anterolateral aspect of the vertebral column exactly where the head of the rib contacts the vertebral body. It is picked up on a

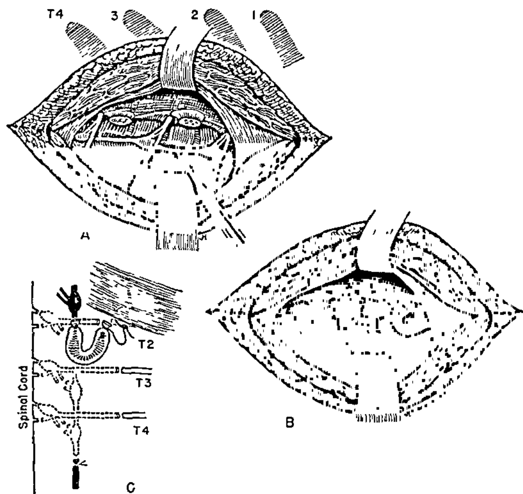


Fig. 79. Thoracic sympathectomy.

The upper extremity can be thoroughly denervated in the great majority of individuals by interrupting the outflow below the first thoracic segment. To guard against regeneration, the anterior roots of the second, third, and fourth segments are resected intraspinally. The trunk is divided below the fourth ganglion. The decentralized second and third ganglia are encased in a silk cylinder, the distal end of which is sutured into the wound. (Reproduced from Smithwick, R H. "The autonomic nervous system," in Cole, W. H *Operative technic in specialty surgery*, Appleton-Century-Crofts, New York, 1949.)

Intratracheal ether-oxygen is the anesthesia of choice, but Beecher (1950) and Gibbon *et al.* (1950) have warned that with the patient in the lateral position, carbon dioxide removal will often be inadequate unless the anesthetist increases pulmonary ventilation by gently compressing the breathing bag to aid spontaneous inspiration. There is a rise in carbon dioxide tension as soon as an anesthetized patient is placed on his side, and this may rise to a dangerous level if the pleura is opened for prolonged periods.

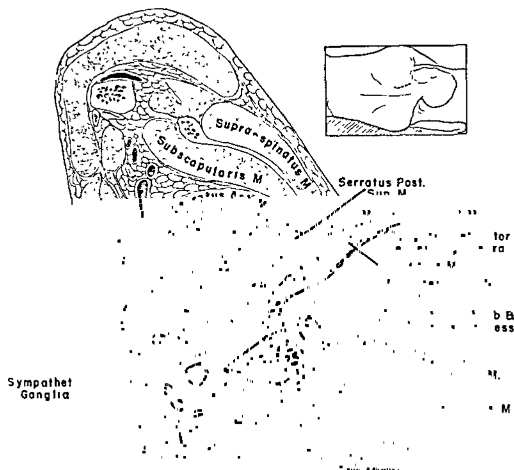


Fig. 81. Cross-sectional view of retropleural exposure of upper thoracic sympathetic chain in lateral-oblique position.

A paravertebral incision 5 cm lateral to the line of spinous processes and placed over the upper four ribs and transverse processes gives a satisfactory exposure for the removal of short sections of the second or second and third ribs Separation of the parietal pleura and exposure of the sympathetic chain are illustrated in Figures 81 and 82. The upper three thoracic ganglia can be excised when only the second rib has been removed. If the patient is not too poor a surgical risk, it is better to remove two ribs and include

excessive dryness of the skin. For this reason it is only necessary to resect the third rib. At the Massachusetts Memorial Hospitals the second and third thoracic ganglia are decentralized as described above. At the Massachusetts General Hospital these two ganglia are resected without any attempt to carry out a further removal of their central connections by resection of the corresponding intercostal nerves with their intraspinal roots. This is such a short and simple procedure that it can be carried out bilaterally at a single stage, using two oblique incisions. Both preganglionic denervation and limited ganglionectomy (T2 and T3) have given satisfactory results in the treatment of severe hyperhidrosis and, by preservation of the first thoracic ganglion, the patient is spared the disfigurement of a Horner's sign.

II. Upper Thoracic Sympathectomy for Cardiac Denervation

The technique of this operation for relief of pain in angina pectoris and the severe uncontrollable tachycardias differs from the procedures described above for vasomotor and sudomotor denervation of the upper extremities. The shortest resection capable of interrupting the major sensory pathways should include the upper three thoracic ganglia, the second to fifth in the case of the cardioaccelerator fibers. More extensive resections from the inferior cervical to the fourth or even fifth thoracic ganglia are preferable, as they reduce the possibility of late recurrence of cardiac pain or tachycardia, or of the persistence of intact fibers in the case of a pre- or post-fixed cardiac outflow.

We believe that the posterior approach gives a better exposure than the supraclavicular route described above and that it is just as safe for the patient with a diseased heart, provided the operation is done in the lateral and not in the prone position. The latter is unphysiological because it limits thoracic inspiration, thereby reducing the negative intrathoracic pressure and effective return of blood to the right side of the heart. Once the surgeon has become accustomed to operating with the patient on his side, he will find it just as easy, while the anesthetist's task is greatly facilitated, as the patient has a better respiratory exchange and is far less likely to have a drop in blood pressure. In placing the patient in the lateral-oblique position, shown in Figure 81, it is important to place a pillow beneath the upper thorax to relieve pressure on the under arm and to support this on an arm board. This arm can then be used for administration of intravenous fluids. The upper arm should be allowed to hang over the edge of the table in order to draw the scapula as far laterally as possible. The blood-pressure cuff is applied to this arm. The patient is steadied on the table by flexing the upper hip and knee, supporting this leg on a pillow, and securing the buttocks in a lateral position by a broad canvas strap.

cases. Peet and Isberg (1946) and Isberg and Peet (1948) have made subsequent reports.

This operation is best carried out in the following manner. A paravertebral incision is made, centered over the eleventh rib. The incision is placed 4 cm lateral to the mid-line and should be 8 cm long. The lateral edge of the sacrospinalis muscle is identified after incising the deep fascia and any underlying fibers of the latissimus dorsi muscle which may be present, as well as the fascia beneath this muscle over the sacrospinalis group. The latter is reflected medially, and the inner 5 cm of the eleventh and twelfth ribs are removed. The pleura is readily reflected digitally from the vertebral column and lower ribs. The sympathetic trunk is identified, and the lower three or four ganglia can be removed. This portion includes the medial rami which form the minor and least splanchnic nerves. The trunk is clipped proximally and distally, as well as all communicating rami. The great splanchnic nerve is readily seen, hooked, clipped, and divided as it penetrates the diaphragm just above the celiac ganglion. The trunk can then be dissected upward. This is best done digitally. A long extent of this should be removed, 15 cm or more, clipping the upper end, or in case it is a fine filament it can be avulsed. The incision is closed carefully, in layers, with interrupted nonabsorbable sutures, the same precautions being observed to aspirate all residual air by means of catheters, as previously described. In hypertensive patients the operation must be bilateral. As has been previously stated, a more extensive exposure and excision is preferable in most hypertensive patients. These operations may be performed in two stages eight to ten days apart, or they can be performed bilaterally at one stage. In visceral pain problems, bilateral procedures may be necessary, but as a rule a longer time interval should intervene between stages. It is felt that the principal field for this technique is in the management of visceral pain in the upper abdomen, as well as in occasional hypertensive patients, particularly those in a very late stage of the disorder, and perhaps in very early cases who are in the stage of intermittent hypertension.

Subdiaphragmatic Splanchnicectomy. This technique for denervation of the splanchnic bed has been described by Craig (1934). It has been utilized largely in the treatment of hypertension but can also be utilized for motor and sensory denervation of the abdominal viscera. In operating for hypertension Craig removed the upper lumbar ganglia as well. The reported results of this operation in hypertensive patients include many which are temporary in nature (E. V. Allen and Adson, 1940). This is presumably due to the limited extent of resection of the great and lesser splanchnic

the inferior cervical and the fourth and fifth thoracic ganglia in the resection, as regeneration of cardiac pain fibers is thereby more effectively prevented.

III. Splanchnicectomy

This operation is most commonly used in connection with the surgical treatment of essential hypertension. It is occasionally used for the relief of abdominal pain (Chap. XIV). Depending upon the technique employed, the motor and sensory innervation of the various abdominal viscera may be partially or completely interrupted. Since the general subject of hypertension has been presented in detail in Chapter XII, this discussion is concerned only with surgical technique.

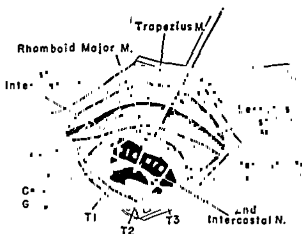


Fig. 82. Exposure of upper thoracic sympathetic ganglia in lateral-oblique position.

Supradiaphragmatic Splanchnicectomy. Peet was the first to use this technique, in which the lower thoracic ganglia and intervening trunk together with the lesser and least splanchnic nerves are removed. In addition, the great splanchnic nerve is resected as extensively as possible. This is carried out on both sides, usually at the same time. The operation does not result in significant postural blood-pressure changes. It is entirely confined to the supradiaphragmatic region, which does not afford opportunity for exploration of the kidneys or adrenal glands. The upper lumbar splanchnic connections cannot be removed, and the twelfth thoracic ganglion is reached with difficulty, if at all. On the basis of clinical results, it appears extensive enough to guard against regeneration. Peet, Woods, and Braden (1940) have reported in detail the effect of this operation in a series of 350

effect a combination of the supradiaphragmatic and subdiaphragmatic techniques. The operative mortality has been low in unselected cases (see Table XXXIV, p. 325), and in recent years has been less than 1 per cent in selected cases. It is performed in two stages eight to ten days apart. Postoperative complications have been rare, the most frequent being hemothorax, usually extrapleural, sufficient to require aspiration in about 5 per cent of the cases. The results of operation have been analyzed and the selection of cases for surgery has been discussed in detail in Chapter XII.

The technique of thoracolumbar sympathectomy is as follows: The patient is placed in the prone position, the chest and pelvis being supported so that there is no pressure upon the abdomen (Fig. 83, A). The table is broken slightly to flatten the lumbar spine. Intratracheal anesthesia should be used. A paravertebral incision is made. The incision is started 3 to 4 cm from the mid-line over the lateral third of the sacrospinalis muscle group and overlying the inner portion of the ninth rib. It runs downward and slightly outward to cross the twelfth rib at the lateral edge of the sacrospinalis muscle, and then continues downward with a slight inward curve to the iliac crest. The dissection is carried down through the deep fascia, through fibers of the latissimus dorsi muscle, with division of the underlying sacrospinalis sheath from the top of the incision to below the twelfth rib. Below this point the deep dissection is carried downward and slightly laterally to the lumbodorsal fascia, incising the deep fascia and a few filaments of the oblique abdominal muscles. The lateral edge of the sacrospinalis muscle is elevated and retracted medially, thereby exposing the underlying eleventh and twelfth ribs (Fig 83, B). A very liberal portion of the former, about 8 cm, should be removed lateral to the transverse process. As a rule, all of the twelfth rib is resected. The eleventh intercostal bundle between is left intact. The twelfth intercostal vessels may be resected if they are in the way in the lower portion of the field (Fig. 83, D), with care not to injure the twelfth nerve which lies in a deeper plane under the lateral edge of the quadratus lumborum muscle. The pleura is separated from the thoracic cage with gentle finger dissection. The latter is best accomplished by working gently inward to the vertebral column, then upward to above the inner end of the eighth rib. The finger is then swept gently laterally and from above downward to the lateral ends of the resected ribs. An incision is then made through the renal fascia just lateral to the diaphragm (Fig. 83, F). The perirenal fat protrudes through this opening.

The fascia is further divided laterally and downward (Fig. 84, A), following which the dissection is carried medially and downward beneath

nerves which this exposure permits. Consequently, regeneration may take place in a comparatively short time. This seems to be the most likely explanation for the temporary character of the effect upon blood pressure. We have had occasion to reoperate upon a number of these patients and have found that the continuity of the great splanchnic nerve had become reestablished within six months to two years after the original procedure. Following secondary operations, the hypertension has again been favorably modified in some cases. In one patient suffering from a neurogenic motor disorder of the colon simulating intestinal obstruction, symptoms were entirely relieved by a bilateral subdiaphragmatic type of splanchnicectomy *in which 3 cm of the great splanchnic nerves were removed in addition to* the lumbar trunks. Seven months later the symptoms suddenly recurred. These were again relieved by a secondary supradiaphragmatic transpleural operation, at which the left great splanchnic nerve was found to be completely regenerated. A few months later, symptoms again recurred and were relieved by a third operation consisting of a transpleural resection of the right great splanchnic nerve. This also was found to have completely regenerated It is our belief that the subdiaphragmatic technique is not a satisfactory operation for denervation of the splanchnic bed.

Thoracolumbar Splanchnicectomy and Sympathectomy. This technique for denervation of the splanchnic bed is one which we have used more than any other in the treatment of hypertension and hypertensive cardiovascular disease. It was first described by one of us (R. H. S) in 1940 and was the outcome of multiple-stage operations. Certain patients in whom previous lesser procedures had been ineffective in modifying the hypertension were subjected to further surgery. After an unsuccessful supradiaphragmatic maneuver in some, the lumbar chains were subsequently removed in two stages, or a bilateral subdiaphragmatic splanchnicectomy was performed. In others a supradiaphragmatic splanchnicectomy was added to a previous subdiaphragmatic procedure. In one case an unsuccessful laminectomy with extensive anterior root section was converted into an excellent result by a secondary thoracolumbar sympathectomy. Thus it was shown that failures could be due to inadequate denervation. It was therefore felt that the statistical chances of a worth-while result would be increased in unselected cases by this more extensive type of operation. As a consequence, it was hoped that eventually our ability to select cases with accuracy would be improved, since other factors affecting the reversibility of the hypertensive state could be better evaluated if failures were not so likely to be due to inadequate denervation. It seemed also that such a procedure would be an additional safeguard against regeneration. This operation is in

this fascial layer and the diaphragm and over the psoas muscle to the lumbar spine. The diaphragm is next divided, together with the adherent underlying fascia between clamps (Fig. 84, B). There are always vessels of consequence in the diaphragm which require ligation. The ascending lumbar and at times the azygos or hemiazygos veins pass through the same hiatus as the trunk. Care must be taken to visualize these so that they are not inadvertently injured, as serious bleeding may result.

After the diaphragm is divided, the table is tilted laterally about 30 deg away from the operator. The kidney and its pedicle are inspected, as well as the adrenal gland. Search for an adrenal tumor should be made at this point. These are found in 3 to 4 per cent of cases, although only an occasional tumor appears to play an active role in maintaining elevated blood pressure. If a tumor is present, it is removed. Unless a dramatic fall in blood pressure ensues immediately, it is best to proceed with splanchnicectomy. The lumbar portion of the trunk is readily palpated and cleared manually of overlying fat and fascia. A narrow Deaver retractor is inserted to displace slightly the psoas muscle. Moist gauze is placed over the kidney and its pedicle, and these are gently retracted downward and outward with a lighted brain spoon or ribbon retractor. The exposure is then complete, the great splanchnic nerve being seen in the lower portion of the thoracic field and ending in the celiac ganglion (Fig. 84, C).

The sympathectomy is begun by elevating the ganglionated chain with a Crile-type nerve hook just below the eleventh ganglion. It is followed downward into the lumbar region. The trunk between the twelfth thoracic and first lumbar ganglia is always very flimsy. The former ganglion and its rami may lie entirely beneath the diaphragm, particularly in patients having a short twelfth rib. There are numerous variations in the anatomy of this region. After experience with splanchnicectomies in over 2,000 cases, we recommend the removal of the sympathetic trunk from the eighth thoracic to the first lumbar ganglia, inclusive, in the ordinary case of hypertension. The second and the third lumbar ganglia may be removed when the postural blood-pressure reflex is unusually active. Evidence for this is an abnormal rise of diastolic pressure, not associated with an abnormal increase in heart rate, when the patient shifts from the horizontal to the upright position. A rise of 20 mm is abnormal, and it usually is corrected by bilateral excision of the first lumbar ganglia. If the rise is greater but less than 40 mm, removal of the second lumbar ganglia on one side seems advisable. For even greater rises the second lumbar ganglia on both sides, and possibly the third as well, should be removed. Ejaculation is usually not affected after removal of both first lumbar ganglia. If, in addition,

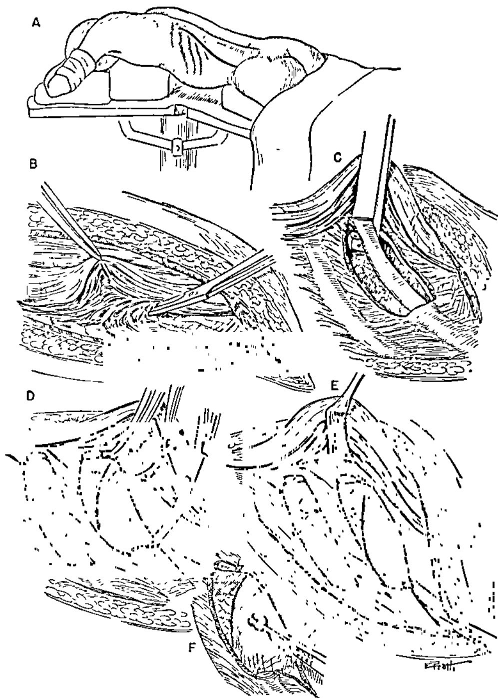


Fig. 83. Thoracolumbar sympathectomy and splanchnicectomy.

1. The splanchnic bed can be thoroughly denervated by thoracolumbar splanchnicectomy. The position of the patient is important. The chest and pelvis are supported upon firm pillows so that there is no pressure upon the abdomen. A paravertebral incision is made, and portions of the eleventh and twelfth ribs are resected. (Reproduced from Smithwick, R H. "The autonomic nervous system," in Cole, W. H. *Operative technic in specialty surgery*, Appleton-Century-Crofts, New York, 1949)

one second lumbar ganglion is removed, about half of the patients may not ejaculate. Orgasm is not affected. Impotence is rare and usually related to incomplete erection. If both second lumbar ganglia are removed, loss of ejaculation occurs in the majority of cases (see p. 399). If male patients insist that ejaculation be preserved at any cost, it is best to stop the downward dissection just above the first lumbar ganglion on one side. We do this occasionally, provided the patient understands that the operation may be less effective, and preferably if they are willing to have the extent of ganglionectomy subsequently increased if it seems advisable. The degree of postural hypotension in the acutely denervated state varies according to the extent of the removal of the lumbar ganglia, being absent or inconsequential if they are left intact, moderate if both first lumbar ganglia are excised, marked if the second lumbar ganglia are removed, and profound if the third are removed on both sides.

The lumbar portion of the operation having been completed, the lower thoracic chain is removed from below upward to include the eighth ganglion in all instances, and occasionally the seventh or the sixth. All rami as well as the trunk proximally and distally are carefully ligated with silk or tantalum clips. It is felt that the portion of the dissection which lies above the ninth ganglion adds nothing to the completeness of the splanchnic denervation but may be an additional safeguard against regeneration. In removing the sympathetic trunk, all of the lesser, least, and upper lumbar splanchnic nerves are necessarily included (Fig. 85).

After resection of the thoracolumbar chain of ganglia, the great splanchnic nerve is elevated upon a hook, crushed, doubly clipped, and divided just above the celiac ganglion. It is then freed upward by manual dissection (Fig. 84, E), with care to avoid injuring the azygos or hemiazygos vein, or the thoracic duct, with which it is intimately associated. If it terminates in the sympathetic trunk at the seventh ganglion, as it occasionally does, the latter is removed and the trunk is clipped proximally. More commonly, a fine strand runs upward, which is best avulsed. Modifications of this technique, which entail the resection of the tenth rib in order to remove additional ganglia, are not regarded as worth while. It is felt that if further surgery is indicated, the remaining portion of the upper thoracic trunk should be removed at a later stage by a fifth rib exposure or by a posterior extrapleural approach. In a number of failures following thoracolumbar sympathectomy this has been carried out, resulting in a total or near-total sympathectomy. To date, this additional procedure has proved ineffective. It is advisable to take a random biopsy from the kidney and the intercostal muscle at the close of the operation (Fig. 86, A) in order to obtain information concerning the state of the renal and peripheral arterioles.

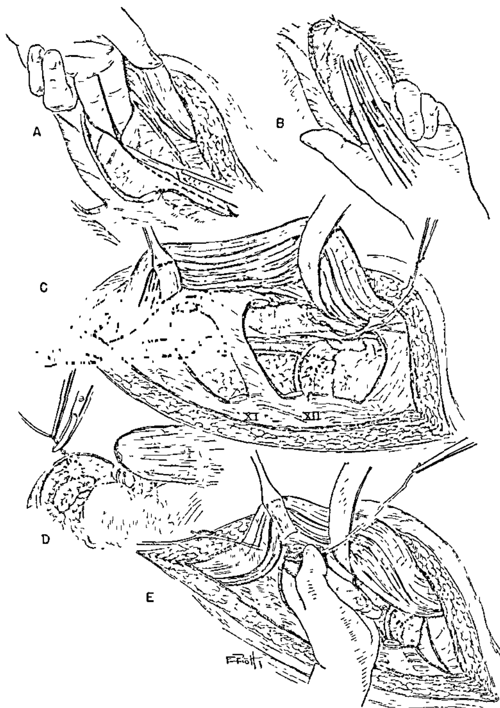


Fig. 84. Thoracolumbar sympathectomy and splanchnicectomy.

2. The diaphragm is divided The adrenal gland and kidney are carefully inspected. If an adrenal tumor is present it should be detected and removed at this point. The sympathetic trunk is removed from T8 to L1 or L2, inclusive, and the great splanchnic nerve is removed from the celiac ganglion to the midthoracic level. (Reproduced from Smithwick, R. H. "The autonomic nervous system," in Cole, W. H. *Operative technic in specialty surgery,* Appleton-Century-Crofts, New York, 1949.)

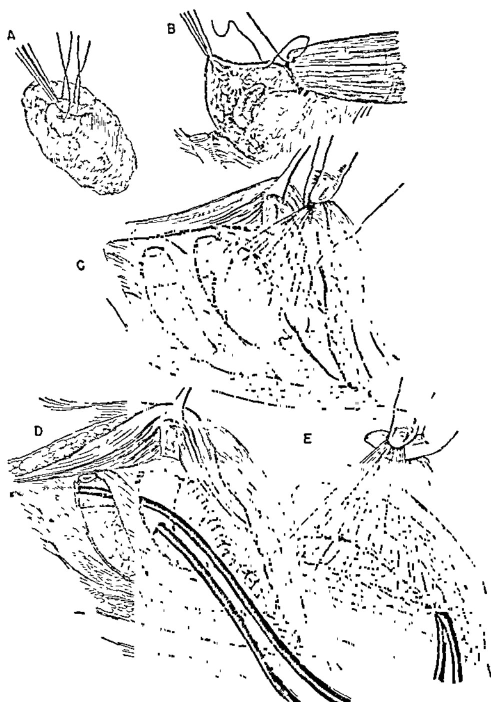


Fig. 86. Thoracolumbar sympathectomy and splanchnicectomy.

3. A kidney biopsy is taken routinely in order to gather information concerning the renal arterioles in hypertensive patients. The diaphragm is resutured, and the wound is closed carefully in layers. Any residual air in the extra- or intrapleural spaces is aspirated, and the catheters are then withdrawn. (Reproduced from Smithwick, R. H. "The autonomic nervous system," in Cole, W. H. *Operative technic in specialty surgery*, Appleton-Century-Crofts, New York, 1949.)

In closing, the diaphragm is resutured, and the renal fascia is approximated with interrupted nonabsorbable sutures (Fig. 86, B, C). A No. 24F catheter is placed in the extrapleural space to aspirate any residual air which may remain after the incision is closed. If there is an opening in the pleura, a second catheter is inserted within the pleural cavity (Fig. 86, D). The lung is expanded with positive pressure, and the catheters are removed, after the incision has been closed in layers with interrupted sutures.

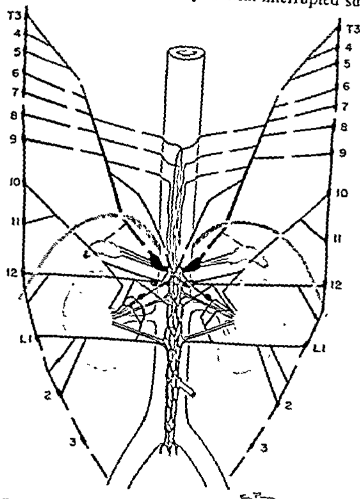


Fig. 85. The nerve supply to the splanchnic bed.
This is generally regarded as arising from the sympathetic trunks from the sixth thoracic to the second lumbar ganglia, inclusive. In occasional cases, filaments which make up the great splanchnic nerve arise from higher levels. Once the great splanchnic trunk is formed, it seems unlikely that visceral fibers of consequence leave it above the eighth thoracic level. The minimal procedure which appears to result consistently in a thorough denervation of the splanchnic bed is bilateral excision of the sympathetic trunks from T8 to L1 inclusive, with excision of the great splanchnic nerves from the celiac ganglia to the midthoracic level. Occasionally, it is desirable to remove the second lumbar ganglia as well, particularly when there is postural hypertension not associated with unusual tachycardia. (Reproduced from Smithwick, R. H., "The surgical treatment of hypertension," in *Advances in Surgery*, Interscience Publishers, Inc., New York, 1949.)

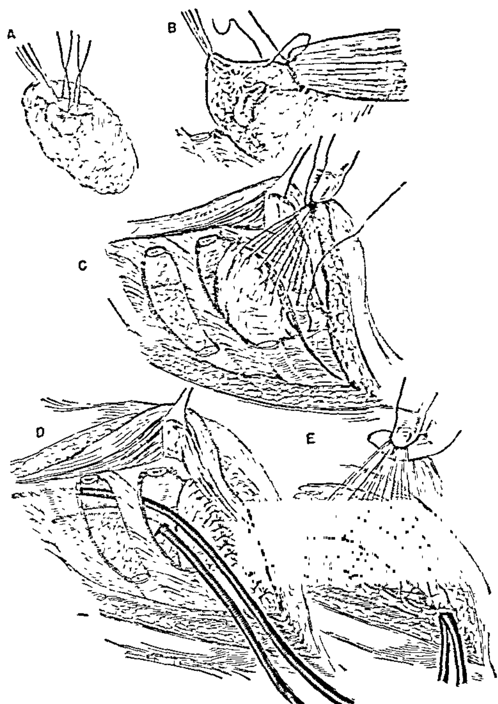


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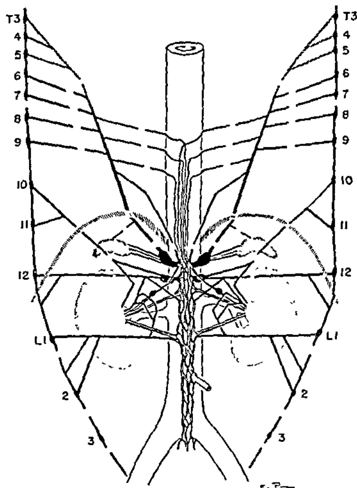


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of this phenomenon. Other late sequelae, such as vasospasm in the undenervated upper extremities, tachycardia, and anginal pain, are discussed in Chapter XII. These may require subsequent further upward extension of the sympathetic denervation, but otherwise the additional surgery has not been found worth while in the treatment of hypertension.

Massachusetts General Hospital Modification of Extrapleural Thoracolumbar Sympathectomy and Splanchnicectomy. In carrying out a thoracolumbar sympathectomy for hypertension or a more limited denervation for pain in intractable disease of the upper abdominal viscera, the surgeons at the Massachusetts General Hospital prefer the lateral to the prone position. As described on page 418, they believe that this permits better respiratory excursion and more effective venous filling of the right side of the heart. One also gains a better exposure of the lumbar ganglia with the patient on his side. This position is illustrated in Figure 87, A. Pressure on the axillary structures is eliminated by a pillow under the upper thorax. The upper leg is flexed at hip and knee and supported on a pillow, while the lower leg is left extended. Webbed canvas straps are adjusted to secure the shoulders and pelvis. By lowering the two ends of the table and laterally flexing the lumbar spine, the lower ribs can be separated from the iliac crest.

A longitudinal paravertebral incision is made 5 cm lateral to the lower thoracic spines and then swung laterally to the center of the iliac crest. The ribs are exposed by dividing the fibers of the trapezius, latissimus dorsi, and serratus posticus inferior muscles. To expose their central articulations, the costal insertions of the erector spinae muscles are cut, and this longitudinal muscle is retracted medially. The entire twelfth rib is then resected, dividing intercostal and diaphragmatic attachments and separating the underlying pleura. We have found it very convenient to use the twelfth rib as a retractor, by elevating its free end and bending it slowly backward some 90 deg and then securing it in this position with a loop of gauze clipped to the drapes (Fig. 87, C). The extra projecting length of rib can be cut off. Prior to closing the incision, this retained central end should be disarticulated.

After the twelfth rib is out of the way, the next step is to open the lumbar fascia, separating the abdominal from the posterior longitudinal muscles. The renal capsule and peritoneum, freed digitally from the quadratus lumborum and psoas muscles, are drawn forward by a broad retractor over a moist gauze pad (Fig. 87, C). In freeing up the under surface of the diaphragm, the twelfth thoracic and first lumbar nerves must be protected against excessive traction, as this leads to postoperative neuralgia. It may

Following the first-stage thoracolumbar sympathectomy, the patients can usually be allowed to sit up briefly with their legs dangling over the side of the bed the day after operation and to get up the next day. No unusual physiological effects are noted. After the second stage, however, the homeostatic adjustment to the upright position is definitely inadequate. Postural hypotension is not noted after lesser operations, and its presence is regarded as conclusive evidence that the splanchnic bed has been thoroughly denervated As has been previously noted, the degree and duration of postural hypotension depends largely upon the extent of removal of the lumbar chain. It is essential that the patients have a well-fitted abdominal girdle with sponge-rubber pads beneath on either side of the lower abdomen. In addition, elastic bandages should be applied from instep to knee when the patients begin to dangle, generally two or three days after the second stage. They can usually sit up in a chair after dangling twice a day for two or three days. After sitting twice a day for several days, they are allowed to walk with an escort. When upright they should be cautioned not to stand still but to walk slowly from one chair to another. Readjustment begins to occur in two or three weeks after operation Following more extensive operations, it may be several months before the point is reached at which the blood pressure does not drop precipitously on standing when supports are removed. The removal is then carried out gradually; after the leg bandages or elastic stockings are dispensed with, the sponge-rubber pads are likewise removed, one at a time, at similar intervals. The snug lower abdominal girdle should be worn for an additional two or three months, sometimes longer

Postoperative discomfort deserves a word of comment. This varies from patient to patient There are two types of pain: One is a superficial girdle variety associated with dysesthesia which is undoubtedly due to operative exposure and irritation of intercostal nerves. Every effort should be made to minimize this by gentleness during operation. Local heat together with the application of Baume Bengué or Nupercaine ointment is helpful. Codeine and salicylates generally have to be used Injecting the exposed eleventh and twelfth intercostal nerves with Dolamin * seems helpful. The other type of pain is deep-seated and crampy, associated with obstipation and loss of appetite. It generally disappears or becomes much less marked in a few weeks. Codeine is the most helpful drug during the height

* Dolamin contains	Benzyl alcohol	7 5 gm
	Ammonium sulfate	7 5 gm
	Sodium chloride	4 8 gm
	Water q s	10 cc with a pH of 7 2

with the tip of a finger or by dissection with a gauze paddy on a curved forceps. In case an extensive splanchnicectomy is to be done, the central end of the eighth rib is also resected, and the pleura is freed from the level of the sixth thoracic vertebra down to the diaphragm. This is similar to the modification described by Poppen (1947).

The thoracic chain and splanchnic nerves are now easily identified as they cross the anterolateral portion of the lower thoracic vertebrae (Fig. 88)

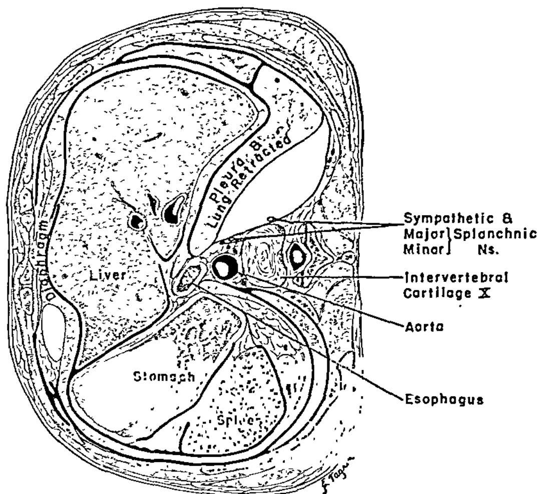


Fig. 88. Position of sympathetic and splanchnic trunks.
Cross section looking upward into the thorax after the pleura has been freed up widely and retracted. The lighted ribbon retractor is not shown.

to pass under the medial arcade of the diaphragm. With a lighted ribbon retractor it is a simple matter to elevate the connecting rami, apply dural clips, and cut them successively from above downward. In this way the ganglionated chain and the major, minor, and least splanchnic trunks can be removed in one piece from the lower half of the thorax and drawn down to the diaphragm.

be better to cut the first lumbar nerve than to preserve it overstretched. At this stage it is a simple matter to inspect the adrenal gland and kidney or to resect the nerves of the renal pedicle in operations for nephralgia.

After the structures beneath the diaphragm have been freed down to its medial arcade, the surgeon should commence detaching the pleura from its upper surface, from under the ribs, and from the bodies of the vertebrae. This thin membrane can usually be separated intact by gentle manipulation

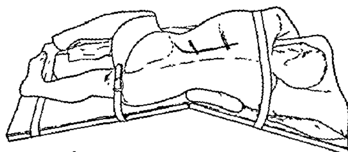


Fig. 87. Technique of thoracolumbar sympathectomy and splanchnicectomy in lateral-oblique position (Massachusetts General Hospital modification).

To simplify the drawing, nerves other than the sympathetic chain and splanchnic trunks (the twelfth thoracic, first lumbar, and genitocrural) are not included in the lower figure.

monly used in sympathectomies for essential hypertension. While it is possible to resect long sections of the sympathetic chain and of the splanchnic nerves by the dorsal extrapleural approach, extensive sympathectomies (from T2 through L2) are most easily accomplished by the transpleural route. With the pleural cavity open, a clear, direct view is obtained through the parietal pleura of the major splanchnic nerve and of most of the rami from which it is formed. When the pleura is incised and lifted off these structures, an excellent anatomical exposure is obtained of the ganglionated chain, the major splanchnic nerve and its rami, the lesser splanchnic, and, after a little further dissection inferiorly, the least splanchnic. These structures can then be removed with anatomic accuracy. We have employed this approach in relatively young individuals in good general condition for whom it was desired to do as extensive an operation as possible for severe hypertension, and for patients in whom the operation was designed to treat not only the hypertension but tachycardia or angina as well.

Intratracheal ether is used for anesthesia. The operation is performed with the patient lying on his side and with the thorax supported from below on a pillow. The arms are held out, and the upper arm is used for a constant intravenous infusion through the veins on the dorsum of the hand or the wrist. The pleura is incised, usually through the bed of the ninth rib, which is removed subperiosteally, stripping the periosteum away from an incision near the upper margin of the rib to avoid the neurovascular bundle. The rib is resected from the tip of the transverse process dorsally to the cartilaginous portion ventrally. The eighth and tenth ribs are then spread apart. When it is desired to reach as high as the second thoracic ganglion, the pleural cavity is opened through the bed of the eighth rib instead of the ninth. The position of the patient and the incision are illustrated in Figure 89, A and B.

In the presence of adhesions, only those attaching the lung to the parietal pleura dorsolaterally are divided. If diaphragmatic adhesions are present, only those located dorsally in the vicinity of the splanchnic nerves and sympathetic trunk need to be divided. It is never necessary to divide the pulmonary ligament. The lung is retracted upward and forward when free of the diaphragm and only forward when diaphragmatic attachments remain. At this stage the major splanchnic nerve and many of its roots can usually be seen through the parietal pleura coursing downward and slightly forward along the lateral aspect of the vertebral column. The ganglionated sympathetic trunk itself can be seen in patients with especially thin pleurae, but in most cases it cannot be seen clearly until the pleura has been lifted off the sympathetic trunk (Fig. 89, B).

The parietal pleura is incised longitudinally along the course of the great

The lumbar chain, which lies at the mesial edge of the psoas muscle adherent to the anterior surface of the vertebral bodies at the edge of the vena cava or aorta, can be exposed exactly as in a lumbar ganglionectomy. In the region between the twelfth thoracic ganglion in the substance of the diaphragm and the first lumbar beneath the crus, where the chain shifts from a lateral to an anterior position on the vertebral bodies, it is often delicate and easily broken. Depending on the ease of exposure, one can either cut across the central tendon of the diaphragm (Figure 87, B) or leave it intact (Fig. 87, C), and then draw the nerves out beneath the medial arcade. The major splanchnic nerve is then clipped and divided as it enters the upper pole of the celiac ganglion, and the lumbar chain is dissected down to the desired level with an unobstructed view.

In the opinion of the surgeons operating at the Massachusetts General Hospital, this approach, which carries the standard exposure for lumbar ganglionectomy up through the diaphragm, is a very simple way of exposing these structures Furthermore, it is possible to gain a more direct high exposure by removing a section of the eighth rib in addition to the twelfth than by the combined removal of the eleventh and twelfth. It has been their impression that removal of both pairs of lower ribs causes mechanical instability of the lumbar spine and is more likely to lead to severe postoperative lumbar neuralgia. This approach has simplified for them the complete resection of the thoracolumbar sympathetic chains from T6 or T8 to L1 or L3 with the entire extent of the splanchnic nerves.

When the dissection has been completed, the central portion of the diaphragm, if it has been cut, is sutured, and the fascial planes and separated muscles are reapproximated with fine cotton stitches. The parietal pleura, which has been widely detached, tends to remain collapsed. To secure re-expansion of the lung, a catheter is left in the extrapleural space and another within the pleura, if it has been opened. The anesthetist applies increased intratracheal pressure as the incision is closed, and any residual air can be aspirated by the surgeon as the catheters are withdrawn.

Various modifications of this operation have been used at the Massachusetts General Hospital since 1946. For sensory denervation of the abdominal viscera there is no need to resect an upper rib, but the ample exposure of the structures beneath the diaphragm is particularly valuable in cases of renal pain when it is desirable to explore the kidney and ureter, and to resect the nerves of the renal pedicle or upper lumbar ganglia in addition to the standard Peet type of splanchnicectomy above the diaphragm.

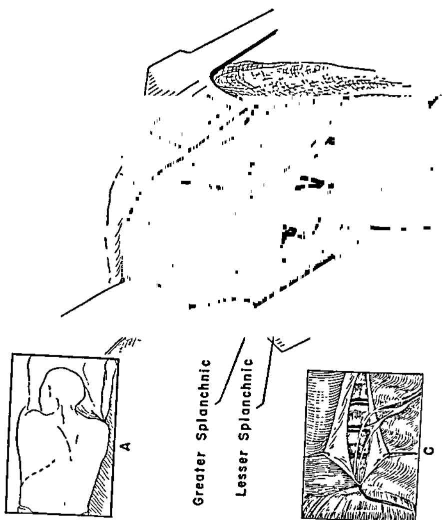
Transpleural Thoracolumbar Sympathectomy and Splanchnicectomy. The extrapleural approach to the splanchnic nerves and thoracolumbar ganglionic chain described in the preceding sections is the technique most com-

monly used in sympathectomies for essential hypertension. While it is possible to resect long sections of the sympathetic chain and of the splanchnic nerves by the dorsal extrapleural approach, extensive sympathectomies (from T2 through L2) are most easily accomplished by the transpleural route. With the pleural cavity open, a clear, direct view is obtained through the parietal pleura of the major splanchnic nerve and of most of the rami from which it is formed. When the pleura is incised and lifted off these structures, an excellent anatomical exposure is obtained of the ganglionated chain, the major splanchnic nerve and its rami, the lesser splanchnic, and, after a little further dissection inferiorly, the least splanchnic. These structures can then be removed with anatomic accuracy. We have employed this approach in relatively young individuals in good general condition for whom it was desired to do as extensive an operation as possible for severe hypertension, and for patients in whom the operation was designed to treat not only the hypertension but tachycardia or angina as well.

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The parietal pleura is incised longitudinally along the course of the great


Greater Splanchnic
Lesser Splanchnic
A
C

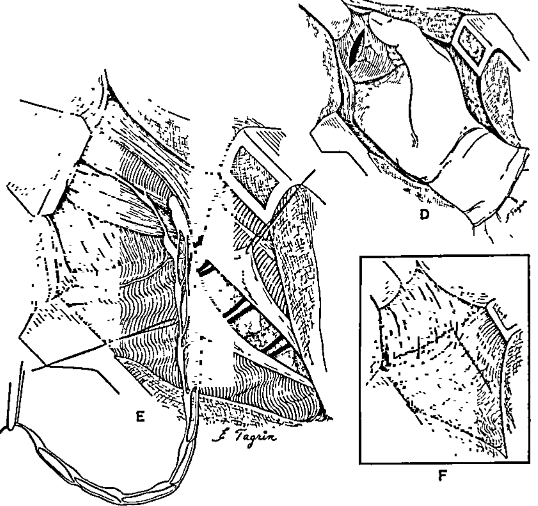


Fig. 89. Technical steps of thoracolumbar sympathectomy by transthoracic approach through bed of ninth rib and parietal pleura.

splanchnic nerve but just lateral to it. Its medial and lateral margins are then lifted off the underlying nerves by blunt dissection. The procedure is carried upward, usually to the fourth thoracic ganglion, but it can be carried to the second ganglion if such an extent is thought desirable in the particular case. The major splanchnic nerve is removed along with the sympathetic chain. It often has rami of origin from as high as the fourth thoracic ganglion. As the dissection is continued caudally, the lesser splanchnic nerve is easily identified, arising from the tenth and eleventh ganglia and passing toward the major splanchnic. The least splanchnic is usually found as a single strand passing medially from the twelfth thoracic ganglion.

It is important to note that between the twelfth thoracic and first lumbar ganglia the sympathetic trunk becomes very tenuous and may be lost if it is not dissected with care. Depending upon the position of the first ganglion below the diaphragm, this portion of the chain may be up to 4 cm in length Furthermore, below the eleventh thoracic ganglion the sympathetic trunk deviates forward from its previous course across the necks of the ribs and comes to lie more anteriorly on the bodies of the lumbar vertebrae. Appreciation of these points will avoid time-consuming search for the lumbar sympathetic chain in the vicinity of the diaphragm.

The diaphragm is next incised, beginning where the splanchnic nerves and the sympathetic chain pass through and beneath it and extending laterally in a slightly curved course parallel with the twelfth rib and about 2 cm from it (Fig. 89, C and D). Through this incision, the perinephric space is opened, exposing the kidney and adrenal. These structures are visualized directly and are palpated. A specimen is taken routinely from the kidney for biopsy (Fig. 89, D). The kidney is then retracted anteromedially, and the nerves are dissected more distally. The major splanchnic nerve is divided about 1 cm proximal to the celiac ganglion and the stump is enclosed, if desired, in a silk cylinder or a tantalum cap. Whether this actually discourages regeneration is a debatable point. The lumbar sympathetic chain is dissected caudally, and its resection can be carried fairly easily below the level of L3, if necessary. In young males it is best to leave the first lumbar ganglion intact at least on one side, in order to preserve ejaculation. Silver dural clips are used for hemostasis and for marking the extent of the resection.

The kidney is then allowed to fall back into its normal position The diaphragm is closed with a single layer of interrupted nonabsorbable sutures (Fig. 89, F), and the parietal pleura is similarly closed. The lung, which was expanded periodically during the procedure, is now fully re-expanded,

and the chest wall is closed in layers. After unilateral sympathectomy the blood pressure falls, but only for a few days. More lasting and severe blood-pressure drops occur when the operation is done on the second side. Dangerous hypotension, actual or relative, is prevented by blood transfusion and by the judicious use of vasoconstrictor substances, such as Neo-synephrine Hydrochloride. We have found it useful to use an intercostal catheter on water seal for the first two days after operation to prevent the accumulation of pleural fluid.

The most annoying feature of the postoperative course after transpleural lumbodorsal sympathectomy has been pain in and near the incision. The incidence of this pain has been higher after transpleural than after extrapleural thoracolumbar sympathectomy. It resembles a severe neuralgia and responds fairly well to physiotherapy, mild analgesics, and camphorated ointment. The pain disappears after two or three weeks, but in rare cases the discomfort has persisted for several months.

IV. Vagectomy: Transpleural Approach

To expose the vagus nerve the seventh or eighth rib is resected from the costal cartilage to the lateral border of the sacrospinalis muscle on the left side. Intratracheal anesthesia is used. The mediastinal pleura is incised from the diaphragm upward to the lung root (Fig. 90). This incision in the pleura is anterior to that for the sympathetic chain. The aorta can be readily palpated, since the vagi are best approached through the left chest. The aorta furnishes a good landmark, the esophagus lying just anterior to it. The pleural incision is made 1 cm anterior to the aorta. It is best to divide the inferior pulmonary ligament in order to mobilize the lower lobe of the lung upward. There are usually one or two small vessels in it which require ligation. The pleural incision to expose the esophagus can be placed where the pulmonary ligament has been separated. After the pleura is incised, the esophagus is readily identified and can be lifted up into view and held by moist tape or rubber wicking. The vagus nerves and their intercommunicating branches form a complicated plexus about the esophagus and are intimately related to its outer coat. The two main trunks and all their ramifications must be identified, freed from the esophagus, and gathered into two bundles, the left or anterior and the right or posterior. These are sectioned below at the diaphragm, crushed and ligated (Fig. 90). The upper 4 or 5 in. of the mobilized plexus can be treated as suggested by Dragstedt and Schafer (1945), that is, ligated distally, transplanted intrapleurally, and not resected. An alternate method is to encase the upper portions in a silk cylinder similar to the technique for dorsal sympathectomy



Fig. 90. Supradiaphragmatic approach to the vagus nerves.

The various steps employed in resecting the supradiaphragmatic portion of the vagus nerves are illustrated. Adequate exposure by the transpleural route is afforded by resecting the seventh and eighth ribs. (For purposes of simplification, only the two main vagal trunks are illustrated. It must be borne in mind that there are often numerous branches which must be searched for and divided.) (Reproduced from Smithwick, R. H. "The autonomic nervous system," in Cole, W. H. *Operative technic in specialty surgery*, Appleton-Century-Crofts, New York, 1949.)

(Fig. 90, D, E). Both of these maneuvers are designed to prevent or minimize regeneration. One may also simply remove several inches of the trunk, ligating them with silk proximally and distally. The pleura is then closed.

It has been suggested that the lower portion of the vagal resection be extended below the diaphragm through an incision in the latter to guard against regeneration. This has not been shown to be necessary, since no evidence of regeneration has as yet been reported. It is perhaps to the point to reiterate at this time that, to be effective, vagectomy must be complete. The chest wound is closed with interrupted nonabsorbable sutures, a catheter being utilized to ensure aspiration of air and full expansion of the lung, as described and illustrated in the technique for thoracolumbar sympathectomy. It is apparent from reports in the literature that vagal resection, as judged by a positive postoperative insulin response, has been incomplete in at least 10 per cent of cases, regardless of whether the operation was carried out through the thorax or the abdomen.

CHAPTER XVIII

Abdominal Sympathectomies

I. Lumbar Sympathetic Ganglionectomy

The lumbar portion of the sympathetic trunk may be approached by either the transperitoneal or the retroperitoneal route. The principal indication for lumbar ganglionectomy is relief of vasospasm of the vessels of the lower extremity in both the presence and the absence of obliterative vascular disease. It is also indicated in the management of the more severe forms of hyperhidrosis, causalgia, and other posttraumatic painful disorders. The operation has a wide field of application, and its use dates back to the observation of Royle (1924*B*), who noted improved circulation in the leg in patients following lumbar ramisectomy for spastic paralysis. Temporary interruption of vasomotor pathways to the leg for diagnostic and therapeutic purposes may be induced by paravertebral procaine block. Alcohol or phenol may also be injected for its more prolonged effect (Chap. XX), but for permanent denervation, surgical resection of the ganglia is so safe and so much more effective that chemical block is rarely used.

A. TRANSPERITONEAL ROUTE

Previous to 1935 we used the transperitoneal approach routinely. It is now used only on the rare occasions when some additional indication for laparotomy exists In the great majority of cases requiring lumbar sympathectomy, a retroperitoneal approach is preferable. Excellent descriptions of the transperitoneal technique have been published by Davis and Kanavel (1926), and Adson and Brown (1925, 1929). The transperitoneal approach is carried out under a general or spinal anesthetic with the patient in the Trendelenburg position. A paramedian incision is made, and the coils of small intestine are gently packed and retained in the upper portion of the abdominal cavity by means of gauze moistened in warm salt solution. The chain on the left is exposed by mobilizing the sigmoid, after cutting across its lateral peritoneal attachment. The sigmoid, together with its vascular supply from the inferior mesenteric artery, is reflected toward the mid-line by freeing its loosely attached mesentery from the posterior abdominal

muscles. This separation is easily effected by the fingers, as in mobilizing the sigmoid prior to its resection in carcinoma of the colon. It is important to identify the ureter and to have an assistant hold the sigmoid and small intestine well out of the way with his hand over a gauze pack. The aorta and upper portion of the left common iliac artery should be clearly exposed. The floor of this incision is formed by the psoas muscle, and its medial wall by the bodies of the lumbar vertebrae and the aorta. The genitocrural nerve runs obliquely downward over the belly of the psoas muscle.

The chain of lumbar ganglia lies just beneath the edge of the aorta in the gutter between the psoas muscle and the vertebrae. It is usually surrounded by a mass of lymphatic trunks and nodes, which at times resemble the chain of sympathetic ganglia. In searching for the sympathetic trunk it is usually best to identify the fourth lumbar ganglion, which lies beneath the edge of the common iliac artery at its bifurcation from the aorta. Once this has been located, the chain should be freed gently by blunt dissection (small cotton pledgets on the end of a hemostat serve well for this purpose). The chain is cut off just above the fourth lumbar ganglion and is grasped in a hemostat. It is then an easy matter to elevate the fibrous sympathetic trunk and to free it from its bed and from the surrounding areolar tissue and lymphatics by careful blunt dissection. The sympathetic rami are divided with scissors as they appear. The trunk itself should be followed upward for a distance of from 6 to 8 cm and cut off above its second lumbar ganglion.

The chain on the right can be exposed either by reflecting the cecum medially, or through an incision in the posterior peritoneum just lateral to the border of the vena cava. This more direct approach cannot be utilized on the left side because the inferior mesenteric artery is in the way. Whichever approach is used, it is most important to identify the ureter and to reflect it forward with the posterior peritoneum. The inferior vena cava is exposed and then retracted gently toward the mid-line. Care must be taken not to injure the lumbar veins, which leave the vena cava and run posteriorly either above or beneath the sympathetic trunk. The trunk itself bears the same relation to the vena cava and the common iliac vein that it bears to the aorta and common iliac artery on the left side. From this point on, resection of the right lumbar ganglia and trunk differs in no way from the procedure on the left side. Resection on the right is slightly more difficult than on the left because of the relative thinness of the vena cava and the presence of lumbar veins arching over the sympathetic chain.

The posterior peritoneal incisions on each side should be sutured with fine catgut as soon as the sympathetic chain has been resected and complete

hemostasis has been assured. The operating table is then dropped back to a horizontal position, all gauze packs are removed, and the intestines are allowed to fall back into the pelvis. The abdominal incision is closed as in any routine laparotomy. It should be possible to complete the bilateral resection within one hour in all but exceptionally fat individuals.

B. RETROPERITONEAL APPROACH—GENERAL CONSIDERATIONS

Various incisions have been suggested for exposure of the lumbar sympathetic trunk by a retroperitoneal approach. Royle (1924*B*), Leriche and Fontaine (1933*C*), Flothow (1935), and Pearl (1937) have published slightly different procedures, all of which are satisfactory. Atlas (1940) uses Pearl's approach but divides the trunk either above or below its third ganglion and then displaces the distal end, burying it in the psoas muscle. Methods of surgical exposure were discussed by Smithwick (1940*A* and *B*) who explained in detail the operative technique and the reasons why, since 1936, we have used the posterior approach in preference to the transperitoneal.

As a rule the lumbar trunk contains four ganglia, but anatomical variations are common (see p. 28). Study of the postoperative effects of interruption of various portions of the lumbar trunk by means of the Victor Minor iodine-starch test had suggested that removal of the first, second, and third lumbar ganglia results in complete sympathetic denervation of the thigh and legs. In recent years, however, postoperative skin-resistance studies by Richter and Otenasek (1946), Ray and Console (1948), and Thompson *et al.* (1950) have shown that, following the removal of the upper three lumbar ganglia, the thigh is not completely denervated in its anterior aspect. This is due to the presence of accessory ganglia (Skoog, 1947) which permit sympathetic motor impulses to reach this area without passing through the lumbar chain. Only by the additional resection of the first and second anterior lumbar roots can the anterior half of the thigh be completely denervated. Fortunately, total denervation of the upper leg is not necessary either in the treatment of vascular disease or in hyperhidrosis. Resection of the second and third lumbar ganglia results in complete denervation of the foot and lower leg except its medial aspect, which is supplied by the saphenous nerve. When it is desirable to obtain a maximal increase in circulation from the knee down, the first lumbar ganglion should be included in the resection. While this operation may seem preferable for the sake of completeness, the first lumbar ganglia should be spared whenever possible in the male lest the power of ejaculation be lost (see p. 399). Both procedures interrupt largely preganglionic fibers running to the leg below the

knee, and both seem extensive enough to give a lasting result. Removal of the fourth ganglion adds nothing to the completeness of the operation, and has the disadvantage of interrupting postganglionic fibers running to the lower leg. Most of these arise in the fourth lumbar and upper two or three sacral ganglia.

Sympathetic denervation of the lower extremity, as described above, is adequate, is largely preganglionic in type, and ensures against a serious degree of regeneration of interrupted vasoconstrictor pathways.* Excision of that portion of the lumbar trunk which includes its first, second, and third ganglia with division of the corresponding communicating rami is the operation of choice for occlusive vascular disease with obliteration of the popliteal pulsation. In less extensive vascular disease or in vasospastic disorders, removal of the second and third lumbar ganglia is adequate. In patients with severe hyperhidrosis or vasospasm without obliterative disease in whom a quadrilateral denervation may be necessary, it is advisable to remove only the third and fourth lumbar ganglia. This restricts the denervation to the distal third of the leg and decreases the compensatory hyperhidrosis in other portions of the body. The clinical results are uniformly satisfactory.

Experience has shown that the lumbar sympathetic trunks are best approached by a posterolateral extraperitoneal route. This approach is far superior to the transperitoneal operation, which we used extensively in the early years. Exposure by laparotomy is a much more difficult task and subjects the patient to unnecessary risk and discomfort. Moreover, it is almost impossible to remove the first lumbar ganglion by this route, and often the second ganglion cannot be reached without difficulty. Frequently, the third and fourth ganglia are removed, a less desirable step except under certain circumstances. The only advantage of the abdominal approach is that both lower extremities can be denervated at the same time. The many advantages of the posterolateral extraperitoneal route far outweigh this. Even in cases where only the second and third lumbar ganglia are to be removed, the anterolateral modification of the retroperitoneal approach is superior to the transperitoneal technique. A bilateral resection can be carried out at one stage if desired; otherwise, the operations are done in two stages spaced about a week apart.

1. Posterolateral Retroperitoneal Approach. Either general or spinal

* In the Massachusetts General Hospital series of 30 lumbar sympathectomies studied for evidence of regeneration by Felder *et al.* (1949) after periods of one to twenty years, 24 per cent had a definite although rarely a clinically significant return of vasoconstriction and 27 per cent had a demonstrable degree of sudomotor activity. These patients had all had resections of the lumbar chain in which two to four ganglia were removed.

anesthesia is used. The latter gives excellent muscular relaxation and perhaps has an advantage in heavily built individuals. Silk-suture technique is preferred. Drainage is never used.

The patient is placed on his side with a kidney bar in place just above the level of the iliac crest. Both knees are drawn upward so that the thighs are approximately at a right angle with the abdomen. This relaxes the iliopsoas muscle group. A medium-sized pillow is placed beneath the under thigh, a second pillow placed between the two thighs, and the under shoulder is drawn forward. All these steps tend to tilt the patient backward toward the operator. This position is maintained by a strap running diagonally over the legs just below the knees and by padded supports placed against the sacrum and the back in the scapular region. The kidney bar is then elevated, widening the space between the twelfth rib and the iliac crest and stretching the external oblique muscle. This effect can be intensified by lowering slightly the head and foot of the table. The final move is to tip the table so that the plane of the patient's back is tilted 30 to 45 deg toward the surgeon, who stands facing the patient's back.

An incision is made starting in the angle formed by the twelfth rib and the sacrospinalis group of muscles (Fig. 91, A). It runs laterally 1 cm below the rib to its tip, then curves downward over the posterior border of the external oblique muscle to the iliac crest. It meets the latter at a point about 3 cm behind the anterosuperior spine of the ilium. In the posterior portion of the incision a variable number of fibers of the latissimus dorsi are cut across The posterior border of the external oblique muscle is dissected out and retracted forward. This exposes the internal oblique muscle and its insertion into the lumbodorsal fascia. The fibers of the muscle and the fascia from which it arises are divided for a distance of 5 cm. This incision is made a finger's breadth below and parallel to the twelfth rib, and should open the lumbodorsal fascia from its origin from the quadratus lumborum and sacrospinalis group of muscles posteriorly to the origin of the transversalis muscle anteriorly. The twelfth intercostal nerve lies just above and the first lumbar nerve just below the incision. The latter can be seen running downward and forward along the lateral border of the quadratus lumborum muscle (Fig. 91, B). A finger is now inserted just below the twelfth rib, over the quadratus lumborum and psoas muscles, and posterior to the lower pole of the kidney and peritoneum. The finger meets the vertebral column in the region of the first lumbar vertebra. The sympathetic trunk is readily palpated on the anterolateral aspect of the spinal column. The finger is gently passed from above downward, separating the peritoneum from the psoas and quadratus lumborum muscles until the trunk has been exposed to a point below its third ganglion.

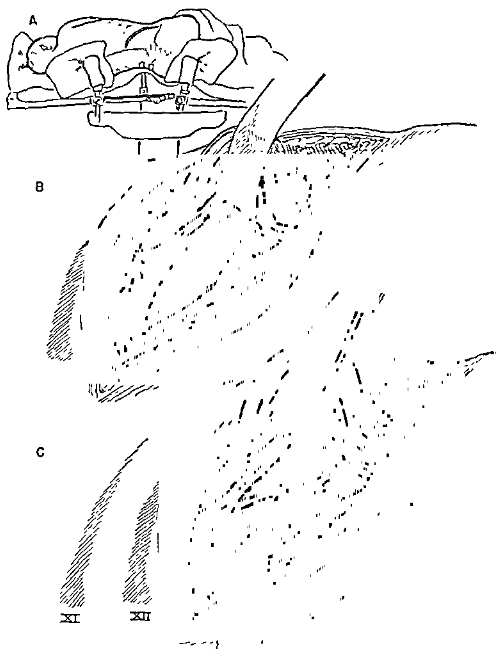


Fig. 91. Lumbar sympathectomy by posterolateral retropleural approach.

This approach is particularly useful if one desires to remove the first lumbar ganglion in addition to others. The vena cava lies just anterior and medial to the lumbar chain and the ureter parallel to it, adherent to the undersurface of the peritoneum. The genitocrural nerve is also often visible, emerging on the ventral surface of the psoas muscle, where it lies parallel and lateral to the sympathetic chain. These structures are illustrated in Fig. 92. (Reproduced from Smithwick, R. H. "The autonomic nervous system," in Cole, W. H. *Operative technic in specialty surgery*, Appleton-Century-Crofts, New York, 1949.)

A long, moist strip of gauze is next inserted against the peritoneum, and the latter, together with the ureter, is then retracted upward and anteriorly with a long curved retractor of the Deaver type (Fig. 92). Because of the

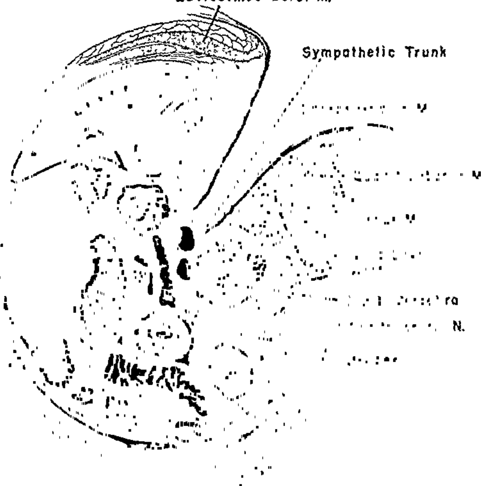


Fig. 92. Posterolateral approach for lumbar sympathectomy.
Cross section to illustrate position of important anatomical structures in relation to the chain of lumbar ganglia.

position of the patient, one can look directly at the sympathetic trunk over the iliopsoas muscle group. It is not necessary to use posterior retraction except for lighting purposes. The sympathetic trunk is plainly visible with its second and third ganglia and sets of communicating rami (Fig. 91, C). The first lumbar ganglion and its rami, as a rule, cannot be seen until the avascular fascia of the medial lumbocostal arch has been divided in an upward direction for about 2 cm. On the right side, lumbar veins running into the vena cava may cross over the trunk. This is particularly true of a

large constant branch just below the communicating ramus of the third lumbar ganglion. The desired portion of the sympathetic trunk and communicating rami can then be readily removed. This step is facilitated by special instruments, long Crile hooks and Hartman forceps being particularly useful.

2. Anterolateral Retroperitoneal Approach. This technique may be used as an alternate to that previously described. It is preferred by many. The principal advantage is that it can be performed bilaterally at a single stage (Fig. 93). The disadvantage is that the exposure is not so satisfactory in heavy-set or obese individuals, the peritoneum has to be reflected more extensively and is much more easily opened, and the upper portion of the lumbar trunk is less accessible. It is most useful when bilateral resection of the second and third, third, or third and fourth ganglia is contemplated. With the patient in the supine position, a transverse incision is made at the level of the umbilicus extending from the lateral border of the rectus muscle to the flank. The superficial fascia and the fascia of the external oblique are divided transversely, including 1 or 2 cm of its muscle fibers in the lateral portion of the wound. The internal oblique muscle is divided in the direction of its fibers for about 8 cm. A similar incision is made in the transversus abdominis muscle. The peritoneum is then carefully separated from the quadratus and psoas muscles, as previously described. It is easy to open the peritoneum and also to get in the wrong plane of cleavage deep to the psoas muscle. Care must be taken not to damage the vena cava and the lumbar veins. More active retraction of the vena cava is needed in this approach, as it overlies the sympathetic trunk. It is also more difficult to be sure what portion of the trunk is being removed by this exposure. There may be some uncertainty on this point in any technique because of the fre-

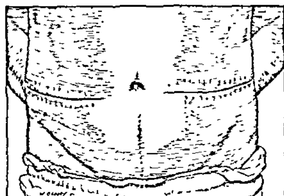


Fig. 93. Lumbar sympathectomy: incisions for anterolateral retroperitoneal approach.

Transverse incisions at the level of the umbilicus, extending from the lateral border of the rectus muscle outward, give a very satisfactory approach to the lumbar portion of the sympathetic trunk. The incision is carried down through the layers of the abdominal wall, splitting the muscles in the direction of the fibers. The peritoneum is carefully reflected to the mid-line over the psoas muscle, thus exposing the sympathetic trunk as it lies on the anterolateral aspect of the lumbar vertebral bodies.

quent anatomical variations which may be encountered. For this reason skin-resistance patterns and surface-temperature studies should be made postoperatively.

The sympathetic trunk is elevated on a long nerve hook, and the desired portion is removed. Silver or tantalum dural clips should be applied to the resected ends of the trunk and to all divided rami. These are readily demonstrable in postoperative films and are useful in confirming the extent and level of the resection. The wound is then closed with interrupted nonabsorbable sutures without drainage. The operation can be performed bilaterally if desired. The postoperative convalescence is usually rapid, and the patients can be up and about the following day and discharged in eight to ten days.

II. Transabdominal Resection of Vagus Nerves

With increasing experience it has become apparent that, in the great majority of cases, the vagus nerves are best approached by the abdominal route. A possible exception is when the operation is to be done for gastrojejunal ulcer following an adequate subtotal gastrectomy. Even then, many surgeons prefer the abdominal exposure to the transthoracic. Incomplete resection of the vagus nerves may, however, result in about 10 per cent of cases. If this occurs following abdominal vagectomy and a secondary resection becomes necessary, the transthoracic exposure is indicated.

Most surgeons prefer a left paramedian incision for the abdominal approach, mobilizing the left lobe of the liver, as indicated by Figure 94. As a matter of fact, a right paramedian incision is very satisfactory, and often through either incision it is not necessary to mobilize the left lobe of the liver. The shortest approach to the esophagus is along the lesser curvature of the stomach, and if one stands on the right of the table and has a right paramedian incision, it rarely will be necessary to mobilize the left lobe of the liver and the exposure is usually excellent. In any case, once an adequate exposure has been obtained, the peritoneum over the esophagus is incised transversely, as shown in Figure 94, B. One can then palpate the esophagus and bring it into view manually, as indicated by Figure 94, C.

It is then best to separate the left or anterior vagus nerve from the esophagus and resect 2 to 4 in. of it, ligating both ends with nonabsorbable suture material. Its position on the anterior part of the esophagus where it joins the stomach is indicated diagrammatically in Figure 95. At this level the right or posterior vagus is best located by digital palpation and lies definitely to the right of the esophagus. It can be drawn out from behind the esophagus and cut on the left side, as indicated in the figure, or it is in

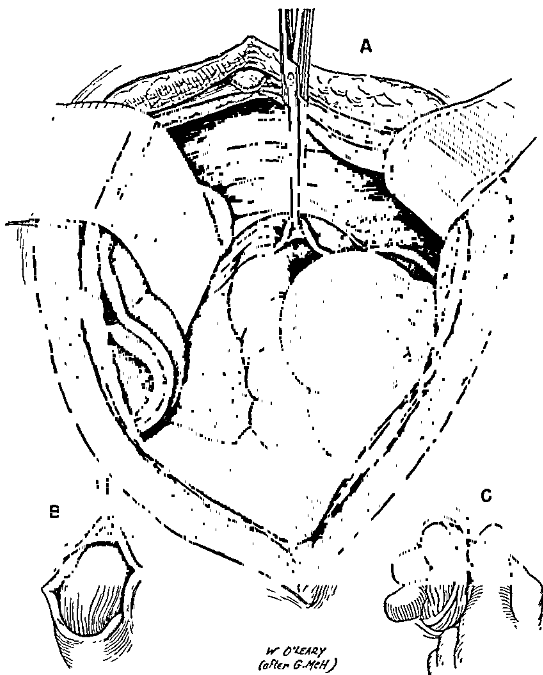


Fig. 94. Transabdominal vagectomy.

1. The abdomen is opened through a high left paramedian incision, and the triangular ligament of the liver is divided. The left lobe of the liver is retracted to the right, the peritoneum over the esophagus at the margin of the diaphragm is divided, and the hiatus is opened. The esophagus is mobilized by careful finger dissection and pulled downward into the abdomen for a distance of 2 to 3 in. (Redrawn from Dragstedt, L. R., Harper, P. V., Jr., Tovee, E. B., and Woodward, E R. "Section of the vagus nerves to the stomach in the treatment of peptic ulcer. Complications and end results after four years." *Ann. Surg.*, 1947, **126:** 687–708, courtesy of J. B. Lippincott Co, Philadelphia.)

most instances equally satisfactory to bring it into view on the right side and section it as it is drawn up anterior to the esophagus. In these figures both vagus nerves are shown as large single trunks. While this anatomical arrangement is sometimes found, in all cases there is also a plexus of smaller

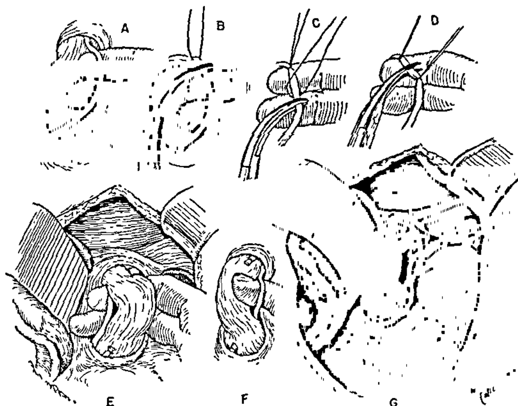


Fig. 95. Transabdominal vagectomy.

2 The vagus nerves are separated from the esophagus by finger dissection, ligated with nonabsorbable suture material, and divided, and a segment 4 to 6 cm in length is excised. (For purposes of simplification only the two main vagal trunks are illustrated. It must be borne in mind that there are often numerous branches which must be searched for and divided.) (Redrawn from Dragstedt, L. R., Harper, P. V., Jr., Tovee, E. B., and Woodward, E. R. "Section of the vagus nerves to the stomach in the treatment of peptic ulcer. Complications and end results after four years." *Ann. Surg.*, 1947, **126**: 687–708, courtesy of J. B. Lippincott Co., Philadelphia)

fibers surrounding the esophagus. In many there may be two or more small fibers taking the place of one or both of the major trunks. The accurate identification of the various nerve fibers is largely dependent upon the sense of touch rather than sight. One learns to feel strands that cannot be easily seen. This should be emphasized, since the 10 per cent incidence of incomplete vagectomies is probably largely due to failure to detect small fibers by palpation. One must also be careful not to damage the wall of the esophagus in separating these fibers from the outer coat. It is quite

possible to carry the dissection too deep and even open the mucosa. T can be sutured quite readily, but it is wise to avoid this complication.

After the nerves are resected, the esophagus drops readily back ir place. As a rule, it is not necessary to resuture the peritoneum over it. Ho ever, if the hiatus is lax or has been unduly dilated during the procedu it is wise to close the peritoneum sufficiently to safeguard against the (velopment of a diaphragmatic hernia. After the nerves have been resect(some additional procedure, most frequently a posterior gastroenterostoı or a partial gastrectomy, will be carried out. The abdominal incision is th closed carefully in layers. In the early postoperative period one must careful to guard against distention of the stomach. This is particularly tı when vagectomy is combined with a gastroenterostomy. Stasis of con quence in the early postoperative period is much less frequently noı when the neurectomy is combined with partial gastrectomy.

III. Resection of Superior Hypogastric Plexus (Presacral Neurectomy)

The technique of resection of the superior hypogastric plexus has be standardized by Cotte (1925) and Learmonth (1931*B*). A left paramedi incision is made from above the umbilicus to within 3 cm of the pubis. T patient is immediately tipped into pronounced Trendelenburg position, ı incision spread open with a self-retaining retractor, and the coils of sm bowel packed into the upper abdomen. The posterior peritoneum is nı incised vertically from a point 2 cm above the bifurcation of the aorta 5 cm below (Fig. 96). Each lip of the peritoneal incision is then retract In this way the superior hemorrhoidal artery is drawn out of the way the left side. In a thin subject the nerves can be readily seen lying ir delicate plexus intermingled with pelvic lymphatics and loose connect tissue. It is best to use blunt dissection and to clean out all the tissue the hollow of the sacrum between the two common iliac arteries. In car ing this out, precautions must be taken not to injure the left common il vein, which lies on the medial side of the artery. Starting just beneath aortic bifurcation, a strand of the presacral plexus is usually found as descends over the left vein. It is picked up on a nerve hook, and as furt strands are identified, first toward the median line and then nearing right common iliac artery, they, in turn, are gathered on the hook.

The apex of the dissected triangle is now cut between the ligatures j above the bifurcation of the aorta. The peripheral end is then grasped b hemostat and freed by blunt dissection with a cotton pledget. Communic ing rami from the lower lumbar ganglia are severed in the process of wip

the plexus off the hollow of the sacrum. The dissection is carried downward until both common iliac arteries and the vein on the left side have been denuded over a length of 5 cm. The base of the triangle is then clamped and ligated. Ligation of the lower end of the pedicle is important in pre-

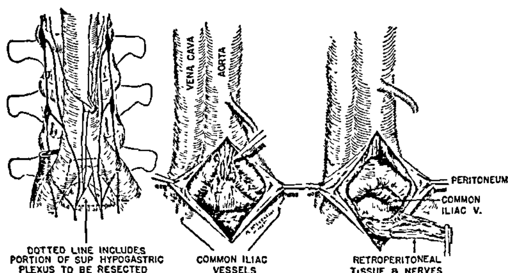


Fig. 96. Resection of the superior hypogastric plexus (presacral neurectomy). (Modified from Adson, A. W., and Masson, J. C. "Dysmenorrhea relieved by resection of presacral sympathetic rami." *J. Amer. med Ass*, 1934, **102**: 986–990, courtesy of American Medical Association, Chicago)

venting seepage of lymph. The posterior peritoneum should be sutured with fine catgut, and the abdominal wall closed in layers in the usual manner. Careful examination of the triangular segment of tissue resected will reveal a variable number of nerve strands which constitute the superior hypogastric plexus.

It is important to remember in male patients that this operation is followed by loss of ejaculation. The power of erection and sensation of orgasm are in no way impaired, so that coitus can still be carried out, but little seminal fluid reaches the prostatic urethra and that tends to back up into the bladder (see p 399). Now that presacral neurectomy in combination with lumbar ganglionectomy for the treatment of megacolon has been superseded by excision of the diseased segment of rectosigmoid, there is rarely any indication for this operation in younger men. In the female where the operation is useful for the relief of idiopathic dysmenorrhea, there is no detectable change in sexual function, except that the uterine contractions in the early stages of labor are painless.

IV. Resection of Inferior Hypogastric Plexus

In order to carry out a complete denervation of the bladder or a peripheral interruption of afferent pathways from the prostate and cervix uteri, it is necessary to cut the terminal rami of the hypogastric ganglia. In this way the sacral autonomic nerves as well as the sympathetic plexuses are destroyed. These ganglia lie in contact with the posterior wall of the rectum. They are so adherent to the wall of the rectum that they cannot be safely excised

Learmonth (1931*B*) described a method for subtotal denervation of the bladder by cutting the anterior branches of the ganglia. As this operation results in complete paralysis of the bladder and forces the patient to a catheter existence, it does not seem worth while to describe its technique. Although the operation is far more efficient than resection of the superior hypogastric plexus in interrupting pain pathways in cases of malignant disease of the bladder, prostate, and cervix, section of the spinothalamic pathways in the spinal cord is a more logical procedure. Cordotomy is also more certain to give complete relief of pain in cases where tumor cells may be infiltrating the lumbosacral plexus, causes less damage to the emptying power of the bladder, and is a less formidable operation.

CHAPTER XIX

Periarterial Sympathectomy and Denervation of Carotid Sinus

Periarterial Sympathectomy. Jaboulay (1899*B*) suggested dissecting the femoral artery from its bed in Scarpa's triangle and division of the vascular nerves which enter its sheath at this level. He stated that trophic ulcers in the feet could be healed by this procedure. His operation was modified by Leriche (1913), who advocated stripping the adventitial sheath of an artery with its perivascular plexus of nerves in order to produce vasodilatation. This type of periarterial sympathectomy has been applied by Leriche to all the larger arterial trunks, and consistently advocated by him and his associate Fontaine (1928, 1930*B*, and 1933*B*) for the treatment of a great variety of circulatory and painful disorders in the extremities. In spite of the enthusiastic reports which have emanated from Strasbourg and other French clinics, perivascular neurectomy has never been extensively adopted by British, German, or American surgeons.* The reasons for this are based on fundamental anatomical and physiological concepts which deserve a thorough explanation.

Anatomical investigations of the vascular innervation conducted by Kramer and Todd (1914), Potts (1914), and more recently by Woollard and Phillips (1932) and Coates (1932) have taught us that the nerve supply to the arteries of the arms and legs, in contrast to that of the vessels in the thorax and abdomen, originates from the mixed peripheral nerves in a segmental manner. Figure 21 shows that these vascular branches leave the main nerve trunks at short intervals and supply the perivascular plexus over a corresponding length of vessel. That this plexus does not run for any great distance down an artery has been shown on histological examination by Kerper (1927), and Busch (1929). In addition, Blair, Duff, and Bingham (1930) made histological sections of the arteries of a human leg amputated after decortication of the femoral artery and found that the

* Handley (1927), Doppler (1931), Herrmann (see Fontaine and Herrmann, 1933), Lehman (1934), and Homans (1940) are the outstanding exceptions.

great majority of the fibers in the perivascular plexus of the lower leg were normal.

Physiological experiments have led to a similar conclusion. L. Rogers and Hemingway (1930) investigated the effect of periarterial sympathectomy by measuring heat elimination in a calorimeter and limb volume in a plethysmograph. Neither of these tests revealed more than a most transitory increase in blood flow. Direct observations of the arteries in rabbits' ears showed a dilatation which lasted less than forty-eight hours. Injection of radiopaque sodium iodide into the aorta of living animals by R. M. Moore, Williams, and Singleton (1933) showed no dilatation of the arterial tree in the leg after periarterial denervation, but a striking increase after lumbar ganglionectomy. Gilding (1932) has brought out the same effect by the intravenous injection of bromophenol blue during electrical stimulation of the stellate ganglion. On the stimulated side, vasoconstriction was so intense that only a small quantity of dye reached the tissue, whereas in the opposite extremity they were deeply stained. On stimulation following periarterial sympathectomy there was no change in the staining reaction, but when a peripheral nerve was cut the vessels relaxed over an area identical to its peripheral distribution. Similar findings have been reported in man by Smithwick and White (1935), who observed that destruction of the peripheral nerves is followed by complete sympathetic paralysis throughout the denervated area.

Leriche (1927*A*) himself was one of the first to recognize these objections and to base the physiological result of periarterial sympathectomy not on the direct interruption of vasoconstrictor nerves but on the division of centripetal sensory fibers. But equally conclusive evidence has been presented against this hypothesis. Anatomically, Stopford (1931) has been unable to prove the existence of ascending sensory fibers in the walls of blood vessels. By physiological investigation Moore and Singleton (1933) have studied the painful reactions that are produced by intra-arterial injection of irritant solutions (lactic acid). The irritant reaction is not altered by arterial decortication or lumbar sympathectomy, but it disappears after cutting the lumbosacral nerves peripheral to the origin of the sympathetic rami even when their sympathetic fibers are left intact. In human subjects Stürup and Carmichael (1935) tested the sensitivity of a digital artery in the little finger after procaine anesthetization of the ulnar nerve in its epicondylar groove. Direct exposure and stimulation of the artery, both by a faradic current and by stretching and clamping, produced no sensory response. The nerve supply of the peripheral vessels is therefore quite different from that of the viscera.

To date, no one has published any convincing demonstration of a durable increase in blood flow in human beings to offset evidence to the contrary in experimental animals. A rise in temperature of as much as 10° F may result for a week following any operation (Fig. 97). This is a nonspecific effect

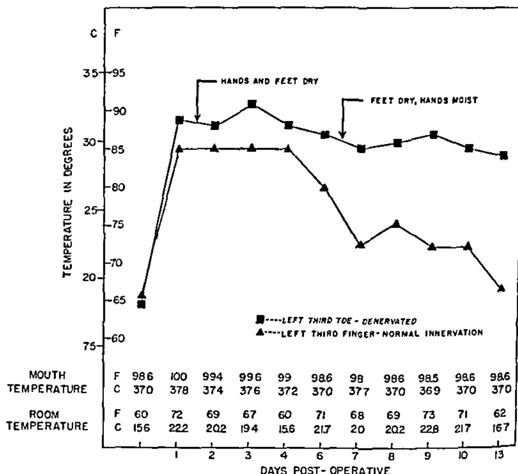


Fig. 97. The vasodilator effect which follows injury to the tissues after any operation.

In this instance bilateral lumbar ganglionectomy has caused a permanent increase in circulation to the feet. Note that during the first four days after operation the hands were equally warmed, and that this nonspecific vasodilator response lasted for a week. These measurements were made in the Massachusetts General Hospital by Dr. Henry L. Heyl.

owing to destruction of tissue and the absorption of the resultant protein decomposition products. A similar but more transitory increase in circulation can be produced by the intravenous injection of a foreign protein, i.e., typhoid vaccine. We have seen the digital ulcerations of Raynaud's disease heal following this procedure. For the treatment of thromboangiitis obliterans or arteriosclerosis with painful gangrene of the foot, temporary interruption of the peripheral nerves gives both a greater and a more lasting

increase in circulation than periarterial sympathectomy, and its effect on pain is likewise more complete (see Smithwick and White, 1935, and Chap. XXI).

From these considerations, as well as from many critical published case reports (see especially Demel, 1930, and G. P. Müller, 1928), and from experiences in this hospital with the periarterial operation in 24 patients (A. W. Allen, 1927), we have been forced to the conclusion that the only indication for periarterial sympathectomy lies in the rare case of traumatic arthritis with pain in the arm (Fontaine and Herrmann, 1933; see p. 226). Although we are fully convinced that the operation is often effective in this condition, it is questionable whether it has any specific effect. We believe that equally beneficial results can be obtained by paravertebral injection of the sympathetic ganglia.

Technique of Periarterial Sympathectomy. Leriche (1927*A*) has given an excellent description of his technique for carrying out periarterial sympathectomy. After exposure of the selected artery under local anesthesia (the femoral in the lower part of Scarpa's triangle, the brachial in the mid upper arm), the common vascular sheath is opened and the artery is freed from its venae comites and neighboring nerves. The adventitia of the artery is then picked up by a pair of fine-toothed forceps and incised longitudinally over a length of 5 cm (Fig. 98, B). Ugo Camera of Turin suggested the infiltration of normal saline under the adventitia to facilitate its separation from the media (Fig. 98, A). This is an excellent procedure and, if procaine is substituted for saline, aids in the anesthesia. One of the lips of the incision is now grasped by a number of fine hemostats, and a blunt dissector is used to detach the outer sheath (Fig. 98, C). After both sides are freed, the artery is lifted up on a small ribbon retractor, and the decortication is completed posteriorly. Bleeding from the vasa vasorum is easily controlled by gauze pressure, but an occasional small arterial branch may require ligation or electrocoagulation. When all the adventitia that can be detached from the resistant plane of the media has been resected, the arterial wall becomes markedly contracted. This is a sign that a thorough decortication has been effected. The periarterial plexus can also be destroyed chemically, either by injecting alcohol beneath the adventitia (Handley, 1927) or by painting the outer coat of the artery with carbolic acid (Doppler, 1931).

Denervation of Carotid Sinus. Carotid sinus denervation involves a periarterial decortication of 2 cm of the common carotid artery below its bifurcation, and of the external and internal carotids for an equal distance above. Particular care must be exercised to ensure a thorough removal of the filaments of the glossopharyngeal (sinus) nerve and the vagal and sym-

pathetic rami which enter the plexus between the origin of the two vessels.

In cases of an irritable sinus, deep ether anesthesia should be supplemented by local procaine block in order to prevent serious disturbances in pulse and blood pressure. Barbiturates such as Pentothal Sodium, with

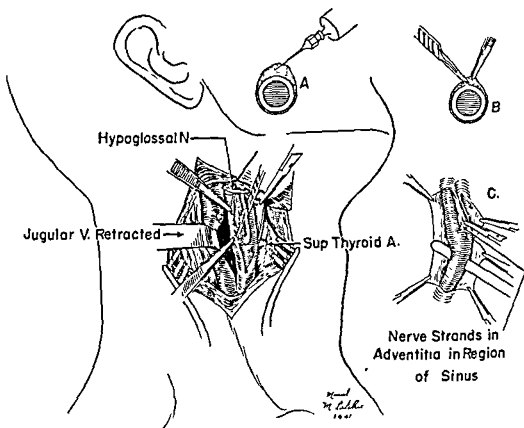


Fig. 98. Denervation of carotid sinus by decortication of common, external, and internal carotid arteries

A. This shows the method of blowing the adventitia off the media by infiltrating procaine solution.

B. This illustrates dissection of adventitia and its nerve fibers from media.

C. The adventitia has been freed, and the carotid body and the sinus nerves are being dissected from the region of the bifurcation.

nitrous oxide, or cyclopropane should never be used, as these compounds fail to decrease sinus irritability (Weese, 1939). An incision centered on the hyoid bone is made along the anterior edge of the sternomastoid muscle, so that the muscle and jugular vein can be retracted posteriorly (Fig. 98). This gives easy access to the carotid artery, which is then separated from the underlying vagus and cervical sympathetic trunk well above and below the bifurcation. After this portion of the common carotid artery and its branches have been freed from neighboring structures, it should be elevated from its bed by traction tapes. Beginning with the common carotid, the

adventitial coat is blown off the media by infiltrating 1 per cent procaine solution between these layers. It is then a simple matter to dissect away the adventitia, although when there is a dilatation of the bulb with calcification of the media, extreme care must be used to avoid a perforation. Stripping of the external and internal carotids is more difficult, because of the deep position of the internal carotid and the numerous branches of the external. Any of these may be ligated, if this facilitates a more thorough decortication. This is particularly true of the ascending pharyngeal artery, which leaves the main trunk right in the area of the carotid sinus. We often prefer to sacrifice the entire external carotid. After its trunk has been ligated and drawn aside, a dissection of this important reflex zone can be carried out. Only by thorough dissection over a wide area of at least 2 cm above and below the bifurcation and of both the anterior and posterior surfaces can the surgeon make certain of securing the desired physiological effect and preventing regeneration. In patients followed many years, we have had no trouble on this score.

CHAPTER XX

Paravertebral Injection of Sympathetic Rami and Ganglia

Paravertebral injection of the sympathetic rami and their ganglia is an extremely valuable therapeutic as well as diagnostic procedure. We are indebted to Läwen (1923) for demonstrating the importance of procaine block in problems of diagnosis, to Brunn and Mandl (1924; also Mandl, 1925*A*, Brunn, 1926) of Vienna for the application of this method to the relief of angina pectoris, and to Swetlow (1926*A*) for introducing alcohol to obtain a lasting chemical block of the sympathetic fibers. More recently, Haxton (1949) and Mandl (1950) have proposed the use of phenol (carbolic acid) in 6 to 10 per cent aqueous solution, and they claim better and more lasting results than with corresponding quantities of alcohol.

During the past twenty-five years diagnostic and therapeutic injection has come into steadily increasing use. As has been stated in Chapter VII, the diagnostic value of paravertebral infiltration with procaine is great, because its temporary paralysis of sympathetic structures enables the surgeon to predict with accuracy the effect of their destruction on peripheral circulation and visceral pain. Furthermore, from the therapeutic point of view, repeated or even single infiltrations of anesthetic drugs may give lasting relief in traumatic arthritis, causalgia, and amputation stump neuralgia (see Chap. IX). In our hands paravertebral alcohol injection is being used in preference to ganglionectomy only in individuals who are extremely poor operative risks. This group is made up for the most part of cases of cardio-aortic pain and advanced malignant disease. Over 100 patients have been submitted to this procedure. The majority have shown as complete and lasting an interruption of visceral pain as if the corresponding ganglia had been excised. In poor-risk cases this method is safer than surgical resection of the ganglia The average patient is up and about on the day after injection, and one medical student, in whom the first and second thoracic ganglia were injected for hyperhidrosis, resumed his class work on the following morning.

Although these results, as a whole, are highly satisfactory, we must

state most emphatically that there is no justification for the routine substitution of alcohol injection for ganglionectomy. In the first place, accurate injection is technically difficult even in thin-backed individuals. The injection must be made at a depth of from 5 to 8 cm and within 5 mm of the nerves to be destroyed. After a primary failure, secondary injections are rarely successful. For these reasons surgeons who are not willing to make a long, careful study of this method are certain to meet with disappointment. A second and more important objection to injection therapy, at least where the thoracic rami are concerned, is that it is frequently followed by an irritative neuralgia. While the fine postganglionic sympathetic fibers may be permanently destroyed,* the neighboring heavily sheathed intercostal nerves undergo a very transitory paralysis. At the end of two to three weeks cutaneous anesthesia is usually replaced by dysesthesia. Depending on the patient's psychic constitution, neuralgia is likely to be more or less troublesome for a period of from one to three months. When ganglionectomy constitutes too great a risk, we do not consider the possibility of postinjection neuralgia to be a serious objection. We do, however, believe that it contraindicates the use of alcohol in the average patient.

In order to produce destruction of the spinal nerves, it is necessary to inject alcohol directly into their sheaths, a procedure which we once recommended for blocking the peripheral nerves in the lower leg (Smithwick and White, 1935). Except in the case of the mandibular and maxillary nerves, this requires surgical exposure, and even then the nerves regenerate completely within a few months. For this reason it is unwise to expect paravertebral injection to relieve pain other than that transmitted over sympathetic pathways. Cardio-aortic pain, for example, can be permanently relieved, whereas pain in carcinoma of the lung, which involves the parietal pleura, is interrupted only as long as the intercostal nerves are paralyzed (a period of several weeks).

Articles Required for Injection. Needles should be made of rustless steel and should be as thin as is consistent with a moderate degree of rigidity.

* Merrick (1941) investigated the effectiveness of alcohol in destroying sympathetic fibers by studying the histological changes in the paravertebral ganglia and rami communicantes of cats. He reported that destruction of the postganglionic neuron cells and permanent degeneration of their axons is possible, provided the alcohol is injected in contact with the ganglia. On the other hand, if the needle is not inserted to a sufficient depth, so that only the rami communicantes are infiltrated, the block is not likely to be permanent because regenerating axons may bridge the zone of scar tissue. As a corollary to this it should follow that permanent destruction of the splanchnic nerves and viscerosensory fibers cannot be achieved by paravertebral injection, because the postganglionic cell stations of the former lie in the scattered preaortic ganglia, and the trophic cells of the latter are situated in the posterior root ganglia. For this reason their axons, which run through the paravertebral ganglia, should be capable of regeneration. Nevertheless, we have had patients under observation for as long as eleven years following alcohol block for angina pectoris without any recurrence of pain.

Twenty-gauge lumbar puncture needles are most satisfactory for paravertebral block. Each needle should be equipped with a depth marker to measure the distance it is to be pushed beneath the rib. A short length of narrow rubber tubing serves this purpose well.

A hypodermic needle for making preliminary intracutaneous infiltrations of procaine at the points of insertion of the larger needles.

Any good 5- to-10-cc glass syringe which fits the needles will serve for injection.

A metal centimeter rule.

Solution of 1 and 2 per cent procaine hydrochloride. (In cases of coronary disease, no adrenaline should be added.)

Ninety-five per cent or absolute ethyl alcohol (C.P.) for permanent block.

As mentioned above, Haxton (1949) has substituted 6 per cent phenol (carbolic acid) in aqueous solution for alcohol and has used it in similar quantities (5 to 10 cc). He claims that 50 cc is well within the toxic dose, that phenol is capable of destroying the ganglion cells in the sympathetic trunks, and that it causes little damage to surrounding tissues. He states that he has been able to obtain satisfactory vasodilatation of the lower extremity, and that in over 8 per cent the effect has been lasting (up to two years). Haxton has not yet applied the method to the upper extremity or used it for cardiosensory denervation. We have had no personal experience to date, but it is quite possible that phenol or some other compound may prove more effective than alcohol.

I. Procaine Block of Cervical Sympathetic Structures

Diagnostic Block of Carotid Sinus Nerves. The technique of this injection has been worked out by Pick and Wertheim (1948). It is important that *no preliminary medication be given, as this is likely to decrease the irritability of the sinus reflex.* The carotid bifurcation lies just in front of the anterior tubercle of the fourth cervical vertebra. While this level may vary slightly in short- and long-necked individuals, this is of no consequence, as procaine diffuses so readily in the fascial plane behind the carotid sheath.

With the neck in slight extension, the transverse line I (Fig. 99, A) is drawn backward from the angle of the mouth coursing over the triturating line of the teeth to the tip of the mastoid. The longitudinal line II is drawn from the condyle of the mandible to the anterior tubercle of C6 vertebra, which can usually be palpated at the posterior border of the sternomastoid muscle. The two lines intersect at 90 deg, and C4 vertebra lies midway between this point and the sixth tubercle. The point of injection is 1 cm anterior to this (Fig. 99, A).

A 5-cm needle with rubber depth marker set at 3 cm is inserted at this point and pushed inward at right angles to the skin. If immediate contact is not made with bone, it can be located by sounding in a slightly upward or downward direction. Once contact with the vertebra has been made, the

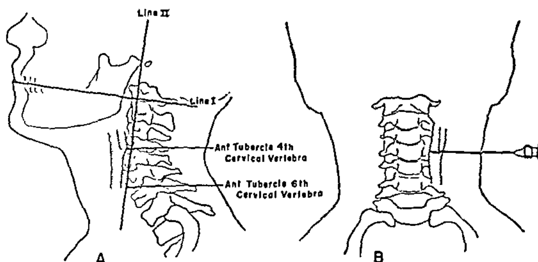


Fig. 99. Injection of carotid sinus nerves by method of Pick and Wertheim. (Redrawn from Pick, J., and Wertheim, H. "A technic for blocking the carotid sinus nerves." *Ann. Surg.*, 1948, 127: 144–149, courtesy of J. B. Lippincott Co., Philadelphia.)

operator should be able to slide his needle anterior to the tubercle 1 cm more without meeting bony resistance. Injection is made at the depth of 4 cm slightly in front of the tubercle of C4 (Fig. 99, B). In this position the needle will have passed through the anterior belly of the sternocleidomastoid muscle, just behind the jugular vein, and will lie in close contact with the posterior portion of the carotid sheath. Transmitted arterial pulsations can usually be felt. After aspiration to make certain that one of the vessels has not been penetrated, 5 to 10 cc of 2 per cent procaine are slowly injected. The sinus compression test is not carried out until the appearance of a Horner's sign indicates infiltration of the cervical sympathetic trunk.

Stellate Ganglion Injection by the Anterior Supraclavicular Route. A number of methods of injecting the stellate ganglion by infiltration against the transverse process of the seventh cervical vertebra from the front or side have been described following the original article by Leriche and Fontaine published in 1934. When the needle is inserted by the supraclavicular anterolateral route, the pleura may be penetrated and pneumothorax will result. In the lateral approach, proposed by Caldwell, Broderick, and Rose (1946), which is a modification of the descending-infiltration

technique of de Sousa Pereira (1945), the needle contacts the sixth rather than the seventh cervical vertebra. By making the puncture at this higher level the hazard of pleural penetration and pneumothorax is greatly reduced, but at the risk of missing an effective interruption of sympathetic fibers to the arm. We have seen an excellent Horner's sign produced, but without any paralysis of the brachial arterioles or sweat glands.

The technique which we prefer is an anterior insertion of the needle against the body of the seventh cervical vertebra. This is certain to place the solution in contact with the cervicothoracic or stellate ganglion without any likelihood of penetrating the pleura, vertebral vessels, or subarachnoid space, complications which can occur when the needle is thrust in from the side of the neck. With the patient in the supine position and his neck extended over a small sandbag, a 5-cm needle is passed through the skin two fingers' breadth above the sternal end of the clavicle and just medial to the sternomastoid tendon (Fig. 100). This is worked inward in the parasagittal plane, passing just lateral to the trachea and esophagus, until bony contact is made with the body of the seventh cervical vertebra. In the average-size adult this will be at a depth of about 3 to 5 cm. The cross-sectional drawing shows that in this position the needle tip lies in the thin belly of the longus colli muscle and in close relation with the cervical sympathetic chain in the prevertebral fascia behind the carotid sheath. Although chances of entering blood vessels like the carotid or vertebral arteries are remote, it is always best to insert the needle without the syringe attached and, when in contact with bone, to make a precautionary aspiration.

Injection of 5 cc of 2 per cent procaine-adrenaline solution should be made slowly. When properly placed, it will soon be followed by congestion of the conjunctiva with the ensuing ptosis and miosis of a Horner's sign. An additional 5 cc can be instilled if there is any reason to doubt that the solution has spread down along the side of the first thoracic vertebra and blocked all the brachial sympathetic rami.

This method, which has been in use by the Massachusetts General Hospital anesthetists for a year, resulted in no complications of any sort in the first 50 trials, save for a single transitory block of the recurrent laryngeal nerve. We consider it by far the easiest and safest method of blocking the brachial or cervical sympathetic fibers, but the solution cannot be counted on to diffuse caudally far enough to ensure a diagnostic block of the cardiosensory or accelerator nerves and, of course, it is unsuitable for therapeutic block with alcohol. For these purposes it is necessary to insert the needles against the sides of the upper thoracic vertebrae by the posterior paravertebral route.

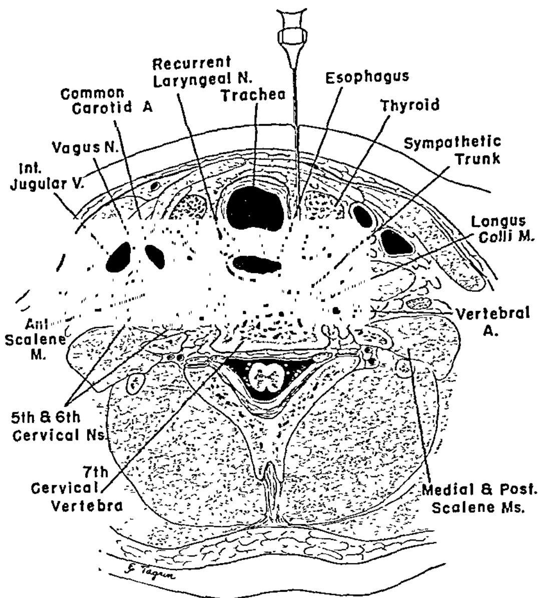


Fig. 100. Injection of cervical sympathetic trunk and stellate ganglion by anterior approach.

II. Paravertebral Injection of the Thoracic Sympathetic Rami and Ganglia *

In carrying out paravertebral injection of the upper thoracic ganglia, it is best to have the patient lying on his side with hips and knees flexed and shoulders at the edge of the bed or X-ray table. The head should be flexed forward and supported on a small pillow so that there will be no lateral curvature of the cervical spine. It is also important to position the

* A large part of the following description is taken from articles by White (1940B) and White and Gentry (1944). We wish to thank the publishers of *Surgery, Gynecology, and Obstetrics* and of the *Journal of Neurosurgery* for their kind authorization to reproduce this material.

patient so that he is not lying on his lower arm, and so that both hands are uncovered and can be observed for vasodilatation and paralysis of sweating.

Injection of alcohol must be performed without a general anesthetic, because this masks the evidence of successful placement of the needles. The patient with angina pectoris must therefore be carefully medicated to enable him to lie for an hour on his side with the minimal amount of discomfort and emotional strain. Having seen two patients die of coronary thrombosis a few hours before the time set for injection, and two others develop infarction during the procedure, we have become sensitized to the danger of psychic strain in persons with severe forms of angina pectoris. It has been shown by Weiss (1929) that barbiturates reduce the chance of toxic reactions to procaine in addition to their effect on emotional stress. Patients are therefore routinely given 3 gr (0.2 gm) of phenobarbital the evening before, and an added similar dose of sodium amytal an hour before injection; $\frac{1}{6}$ to $\frac{1}{4}$ grain (10 to 15 mg) morphine sulfate s.c. is ordered before the patient is moved to the operating room. It is also safer to administer $\frac{1}{100}$ gr (0.6 mg) of atropine sulfate subcutaneously as a protection against syncope and other vagal reflexes. If, on arrival in the operating room, the patient is still restless and worried, an additional small dose of morphine or barbiturate should be given intravenously before inserting the needles. In any event, morphine should be available in a syringe for immediate intravenous injection in case the patient develops any severe pain during the course of the procedure.

The method of checking the exact position of the needles by X-ray control, developed by White and Gentry (1944), has proved to be of great help in accurate injection. All that is necessary is to place the X-ray cassette in position for a lateral film of the cervicothoracic spine prior to injection and to make the exposure with a portable tube after the needles have been inserted.

The bony landmarks for paravertebral injection are the spinous processes. Owing to their imbrication like the shingles on a roof, the tip of each marks the level of the transverse process and the posterior angle of the rib next below. Thus, the highest prominent vertebral spine, the seventh cervical, marks the level of the first rib; this relationship holds over the entire length of the thoracic vertebrae. In thin individuals it is a very simple matter to locate the spines, but in the stocky type which so often goes with angina pectoris, this may be a difficult matter. The points of injection are marked 4 cm lateral to the spinous processes (Fig. 101). Following the use of tincture of iodine, acriflavine applied with a fine cotton applicator is an

excellent marking medium, as the two substances combine to form a jet-black sterile mark.

The technique of inserting the needles is essentially Labat's (1930) second method of paravertebral injection. Procaine is first injected intradermally 4 cm lateral to the thoracic spines. Ten-centimeter needles (with depth markers on the shafts) are then inserted at these points and pushed inward perpendicularly to the skin until the transverse process or the articulating portion of the rib is touched at an average depth of from 2 to 5 cm (Fig. 102, first position of needle). It is important to visualize the depth of the ribs in order not to penetrate the pleura and puncture the surface of the lung. If this happens, a spontaneous pneumothorax occasionally develops in the course of a few hours. Once contact has been made with bone, the tip of the needle is manipulated caudally until it touches the lower border of the transverse process. The depth marker is then pulled out to a distance of 3 cm from the skin. Each needle is now inclined to an angle of approximately 20 deg with the median sagittal plane and perpendicular to the curvature of the back in relation to the long axis of the thorax. When thrust inward on this bearing, a second contact is usually made with bone at a further depth of 3 cm (Fig. 102, second position of needle). If sooner, the needle must be withdrawn and reinserted at a slightly lesser angle. On the other hand, if no contact is made at 3 cm, the needle must be directed further toward the mid-line. The paravertebral gangliated chains lie at an average depth of 3 cm beneath the transverse processes, running along the anterolateral surface of the vertebral bodies and looping over the heads of the ribs. The further forward the tips of the needles can be inserted and still maintain their contact with bone, the less alcohol will come in contact with the intercostal nerves, and the greater amount will surround the gray visceral rami which run forward from the sympathetic trunk to the heart. A useful trick in working the tip of a needle forward

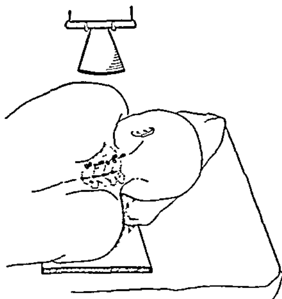


Fig. 101. Paravertebral injection of upper thoracic sympathetic ganglia.
1. Position of patient for X-ray verification of correct insertion of needles.

alongside the vertebra is to start with the beveled tip pointed medially. When bone is touched, the tip of the needle can often be made to scrape along it if the needle is rotated through 180 deg so that its beveled tip is turned away from the bone. A depth of even 4 cm beneath the transverse

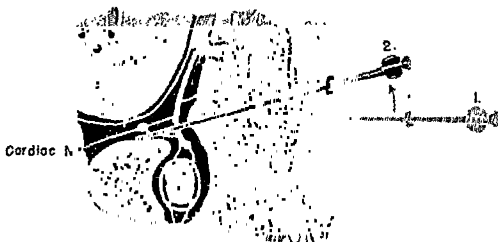


Fig. 102. Paravertebral injection of upper thoracic sympathetic ganglia. 2. Insertion of needle for injection of cardiac nerves: *1*. Needle inserted 4 cm to left of spinous process and tip in contact with transverse process of vertebra. Depth marker has been set at a point 3 cm from the skin. *2*. Shank of needle has been rotated outward and tip worked inward until, at an additional depth of 3 cm, it lies in contact with the side of the vertebra and in close approximation with the gangliotated sympathetic chain (Reproduced from White, J. C. "Technique of paravertebral alcohol injection: Methods and safeguards in its use in the treatment of angina pectoris," by permission of *Surgery, Gynecology and Obstetrics*, Chicago, 1940, 71: 334–343.)

process is quite safe, provided the tip of the needle still rests against bone, and injection of sclerosing solution at this depth is almost certain to destroy the visceral rami. An infiltration in this region will diffuse freely through the retropleural space, bathing the spinal nerves, the sympathetic trunk and its rami, and the cardiac nerves which run anteriorly into the posterior mediastinum (Fig 103).

In performing these injections, the needles should never be attached to the syringe Care should be taken that the tip of a needle does not lie within the pleural space, in a blood vessel, or in an outward prolongation of the subarachnoid space. None of these eventualities is dangerous provided it is recognized and the position of the needle is corrected. With the tip touching bone, it is almost impossible for the solution to leak into the pleural cavity Rapid aspiration of procaine placed in the butt of the needle, or a cough reflex on injection, indicates that the tip lies within the pleura. If it lies within a blood vessel or a lateral prolongation of the

subarachnoid space, aspiration of blood or spinal fluid will make these complications obvious. Bloody taps are frequent under the upper two ribs, because the intercostal branch of the costocervical artery parallels the first and second thoracic ganglia. Spinal fluid is more rarely aspirated, but the possibility of a high spinal injection of either procaine or alcohol is a serious matter. We have withdrawn spinal fluid twice, and we know of 5 instances of intrathecal injection of either procaine or alcohol. When all of the needles have been properly placed they should form a characteristic pattern with their shafts lying in the same sagittal plane. In injecting the cardiac plexus (T1 to T4), the uppermost needle should be inserted deepest. Its shaft should parallel the others and not point in a more caudal direction, otherwise its tip will be certain to contact the second rather than the first thoracic vertebra.

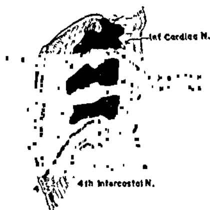


Fig. 103. Distribution of 2 cc of methylene blue injected against the sides of the upper three thoracic vertebrae in a cadaver.

The dissection shows the way solutions diffuse in the retropleural plane around the sympathetic ganglia, communicant rami, cardiac, and intercostal nerves. (Reproduced from White, J. C. "Technique of paravertebral alcohol injection: Methods and safeguards in its use in the treatment of angina pectoris," by permission of *Surgery, Gynecology and Obstetrics*, Chicago, 1940, **71**: 334–343.)

When the lower thoracic ganglia and splanchnic rami are to be injected, the technique for inserting the needles is exactly similar. Go in 4 cm lateral to the appropriate spinous processes and work the needles inward and forward in the retropleural space a good 3 cm to a position in contact with the anterolateral surface of the vertebra.

In order to inject alcohol and produce a lasting chemical destruction of the visceral nerves, a special technique has been developed As mentioned above, an X-ray cassette has been placed beneath the patient's cervicothoracic spine before inserting the needles. Once these are in place, the patient's shoulders and trunk are adjusted to a true lateral position, and the film is exposed by a portable X-ray tube. If the needles are not shown to lie in a satisfactory position well anterior and against the sides of the vertebrae, their position is adjusted and checked by a second X ray. While it is unnecessary for the skillful operator to use X-ray control in simple diagnostic block, when large quantities of procaine can be used, we insist on its use in every case when alcohol is to be injected.

In cases of cardioaortic pain,* 2 cc of 2 per cent procaine solution without adrenaline is first injected through each needle. If properly placed, this minimal amount of solution produces clear-cut signs of intercostal and sympathetic nerve paralysis within a period of five to ten minutes. Anesthesia appears in the axilla and over the third and fourth ribs front and back. No anesthesia develops over the first and second ribs, as this area is also innervated by descending branches of the third and fourth cervical nerves. No anesthesia should develop in the arm or hand, but this entire region, as well as the side of the neck and face, should become hot and dry. This unilateral sympathetic paralysis is particularly striking when the hands are cold or sweaty from nervousness. Horner's syndrome is a less reliable sign, as it is often hard to make out with the patient lying on his side and with the pupils constricted after morphine. When these signs appear rapidly, it is good evidence that the needle tips lie close to the sympathetic trunk. If they fail to develop within ten minutes, it is best to withdraw the needles and reinsert them at a later time It must be borne in mind that procaine diffuses through the tissues far more readily than does alcohol, and experience has shown that unless a clear-cut block can be produced by a minimal quantity there is no assurance of a lasting paralysis with 5 cc of alcohol. †

When the needles have been placed correctly and there is no anesthesia of the ulnar nerve or evidence of subarachnoid block, it is advisable to inject a further 3 cc of 1 per cent procaine into each. This supplementary infiltration is to ensure a widespread anesthesia, so that the final injection of alcohol will be painless. The additional dilution of the alcohol does not seem to prevent an effective destruction of nerve tissue.

The final injection of 95 per cent alcohol is carried out very slowly, a total of 5 cc being injected into each needle, but it is important to draw back on the plunger after each half cubic centimeter has run in to make sure that the needle tip cannot have shifted and penetrated a blood vessel or the subarachnoid space. Several minutes should be spent in injecting the alcohol through each needle. If the patient complains of any undue discomfort, the injection must be stopped for a few minutes until the pain subsides. By following the alcohol with a few drops of Lipiodol or Pantopaque, the exact area of injection can be identified by subsequent anterior-posterior and lateral spinal X rays (Fig. 54). This is of great value in developing

* The procedure described below is for use in angina pectoris, as it is used most frequently for this purpose. The procedure for injecting the lower thoracic ganglia and splanchnic rami is essentially the same.

† Five cubic centimeters of alcohol injected into the thigh muscle of a rabbit causes an area of necrosis little over 1 cm in diameter.

the technical skill of the operator and in discovering the cause of failures. Before we adopted the routine use of X-ray verification of the position of the needles, it was often found that the highest point of injection lay alongside the second thoracic vertebra, but it is important to infiltrate the rami at the side of the first. In the thick-backed individual it is difficult to identify the first rib. As it is most undesirable to inject alcohol above it in the region of the brachial plexus, one is often forced to play safe and select the lower of two doubtful points. On several occasions when anginal attacks have persisted in the arm and under the upper sternum, subsequent X rays have shown no Lipiodol above the second thoracic vertebra. This residual pain has disappeared after a more accurate injection under the first rib made possible by X-ray localization.

After the needles have been withdrawn, the patient should be kept on his side with his back supported by a pillow and as quiet as possible for an hour or more in order to minimize diffusion of the alcohol. He may then be shifted over onto his back, and after two hours allowed to assume any desired position in bed. Most patients can be up by the next morning and leave the hospital within a day or two.

Complications. At the Massachusetts General Hospital early postinjection complications in a series of over 100 injections have been limited to:

1. One case of severe pleuritic pain, which required large doses of morphine and lasted six hours. This was probably due to some alcohol leaking into the pleural cavity.

2. Several cases of transitory mild pleuritic pain, which developed a few hours after injection as the procaine was absorbed. This required chest strapping and morphine in several instances, but in all but one patient it disappeared overnight.

3. One case of pneumonia which occurred in a woman of eighty-five dying of coronary infarction. Alcohol was injected to relieve unbearable pain.

4. Three cases of pneumothorax, which were caused by a needle perforating the pleura and causing slow leaks of air from injured alveoli. One of these required subsequent aspiration of the air.

Although no instance of intrathecal injection of alcohol has occurred in this series, such an accident has been reported by Molitch and Wilson (1931) and resulted in a Brown-Séquard paralysis, which fortunately cleared up. Precautions which can be taken to avoid this most serious complication are: Never slide the needle over the upper border of a rib in a cephalad direction; always insert the needle detached from the syringe, and draw back on the plunger at frequent intervals during the actual in-

jection. In spite of these precautions, we have witnessed high spinal anesthesia on three occasions in the course of paravertebral procaine injection However, if a volume of only 2 cc of 2 per cent solution is used as a test for the position of each needle, the risk of injecting this small amount (40 mg) is slight.

Late complications have consisted of intercostal irritation and neuralgia The sympathetic ganglia lie so close to the intercostal nerves that alcohol infiltrated around the chain cannot help bathing their trunks. They are paralyzed at first, but anesthesia begins to disappear in their anterior divisions within a fortnight. Within a month the intercostal nerves are recovering along their entire length, and with this there is a greater or lesser degree of dysesthesia of the chest wall, which commonly persists for a number of months. Most patients state that pressure of clothing irritates the tender skin, and that there is a burning sensation with occasional shooting pains. In most cases the discomfort is quite bearable and clears up in a month or two. In others (about 10 per cent) it is really troublesome and requires mild sedation with acetylsalicylic acid or Empirin Compound, phenobarbital at night, and occasional doses of codeine. Baking the hypersensitive areas is often helpful. With the exception of a neurotic woman and two other individuals in whom the injection failed to relieve the anginal attacks, all the patients have stated that they would willingly submit to a second injection if their pain should recur.

There is no question that postinjection neuralgia constitutes a serious objection to alcohol block. In advanced coronary and malignant disease its disadvantages are far less than the risk of mortality from operation, but it limits the application of the method to the more severe cases

Duration of Sympathetic Paralysis. While alcohol causes only a transitory paralysis of the heavily sheathed intercostal nerves, it most frequently produces a permanent interruption of the afferent pathways of visceral pain We have 1 patient under observation who has had relief of attacks of angina pectoris in the precordium and arm for over eleven years, and 17 others without recurrence over periods ranging from one to seven years. Evidence of regeneration of cardiosensory fibers has been observed in less than a fifth of the cases treated by injection. A patient with an intensely painful aortic aneurysm was relieved of pain for five years. In the attempt to secure a permanent vasomotor paralysis we have been less successful. A few of these individuals have shown as satisfactory results at the end of a year as after the average cervicothoracic ganglionectomy, but more frequently there has been a recurrence of sympathetic motor function at the end of six months These findings are in agreement with results published from other clinics (Flothow, 1931; Reichert, 1933).

III. Paravertebral Injection of the Lumbar Sympathetic Rami and Ganglia

In lumbar as in thoracic paravertebral injection, the spinous processes constitute the important bony landmarks. A transverse line drawn tangent to the upper edge of the spinous process of any lumbar vertebra marks the level of its transverse process. Unlike the thoracic spines, which point obliquely downward and are imbricated one over the other, the lumbar spinous processes are separate vertical blades of bone which project 2 to 3 cm above the vertebral lamina. Except in unusually stout patients, their tips are easily palpated; they measure from 1.5 to 2.5 cm in height and about 5mm in thickness. There is a well-marked depression about 0.5 cm long between each two lumbar spines. The method of identifying the individual processes is shown in Figure 104.

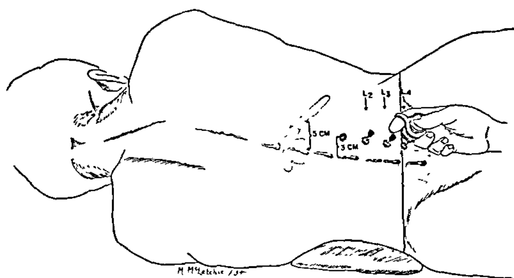


Fig. 104. Paravertebral injection of lumbar sympathetic ganglia.
1 Bony landmarks for inserting needles.

Injection can be made with the patient lying flat on his abdomen or turned on the side opposite the one to be injected. In the technique described by Labat (1930), needles 8 to 10 cm in length are inserted through the skin 3 cm lateral to the upper edge of each lumbar spine. When pushed perpendicularly inward to a depth of 3 to 4 cm, they should make contact with the transverse process of the same vertebra. If bone is not felt at this depth, the direction of the needle must be slightly altered, either upward or downward. After the transverse process has been located, the needle is pointed slightly upward to pass above the transverse process and inward at a slight angle toward the mid-line. It is then thrust slowly down through the psoas muscle until its tip can be felt scraping along the edge

of the vertebra * (Fig. 105). A rubber marker is of great assistance in measuring the correct depth. Injection made against the sides of the vertebrae and 2.5 to 3.5 cm beneath their transverse processes will result in a thorough blocking of the sympathetic rami and the corresponding ganglia, with little if any infiltration of the lumbar nerves.

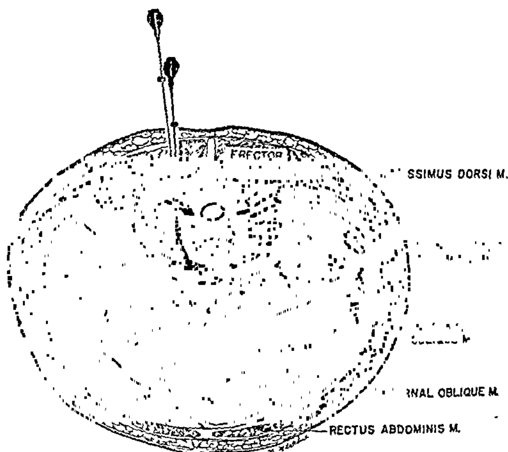


Fig. 105. Paravertebral injection of lumbar sympathetic ganglia. 2. Method of inserting needles.

In order to block the second to fourth lumbar ganglia, we have inserted needles above the three lower lumbar transverse processes. As in the thoracic region, it is important to insert the needles separate from the syringe, to place their tips against the bony sides of the vertebrae, and then to aspirate each in turn before injection. By observing these precautions, the danger of injecting procaine or alcohol into a blood vessel or the subarachnoid space can be averted. Procaine-adrenaline solution should then be injected through each needle. The rapid warming and drying of the

* As the lumbar nerves lie midway between the transverse processes, the needles must be advanced slowly and their direction changed if paresthesias are produced

corresponding foot is proof that the needles are accurately placed. With such a deep injection there is commonly only partial anesthesia of the skin in the back, the side of the buttock, and over the distribution of the genitofemoral, anterior femoral, and lateral femoral cutaneous nerves.

If alcohol is to be injected to obtain a lasting block, a lateral X-ray film should be taken first to check the position of the needles. Only a small amount of procaine (2.5 cc) should be injected at first to make doubly sure that the needles are in close approximation to the sympathetic trunks on the anterolateral surface of the vertebral bodies. Then, if signs of sympathetic paralysis fail to develop, it is best not to attempt any readjustment of the needles or further infiltration of anesthetic solution because of the danger that larger quantities of procaine will paralyze nerves beyond the zone which can be destroyed by alcohol. Under these circumstances it is advisable to give up for the moment and attempt the injection again at a later date.

After the needles are accurately placed, another 3 cc of 1 per cent procaine should be infiltrated through each in order to ensure thorough anesthetization of the tissues; this should be followed by 4 to 5 cc of 95 per cent alcohol. If this is run in at a very slow rate and interrupted for a few minutes on the slightest sign of pain, it is usually possible to carry out the injection with very little discomfort to the patient. Injection of 0.25 cc of Lipiodol before withdrawing the needles enables a valuable X-ray check to be made on the position of the alcohol. After injection the patient should be kept quiet for several hours to prevent diffusion of the alcohol by muscular movements. There is, however, no need to keep him in bed on the following morning nor in the hospital for more than a day or two.

Haxton (1949) has advocated the substitution of an aqueous solution of 6 to 10 percent phenol for alcohol, as he has found that this more destructive compound actually kills the ganglion cells. We have had no experience with this method, but Haxton has used it in over 200 cases of circulatory disorders with long-lasting vasomotor paralysis and few complications.

Neuralgia is rare after lumbar paravertebral injection because the chemical sclerosing agent is injected several centimeters in front of the lumbar nerves and is separated from them by the psoas muscle. Our only complications with alcohol have been transitory psoas weakness and a bedsore in an early case. In this instance a patient who was relieved of unbearable pain from embolism of the common iliac artery developed extensive anesthesia of the buttock. This complication can usually be avoided if cutaneous anesthesia is searched for and care is taken to keep the patient's

of the vertebra * (Fig. 105). A rubber marker is of great assistance in measuring the correct depth. Injection made against the sides of the vertebrae and 2.5 to 3.5 cm beneath their transverse processes will result in a thorough blocking of the sympathetic rami and the corresponding ganglia, *with little if any infiltration of the lumbar nerves.*

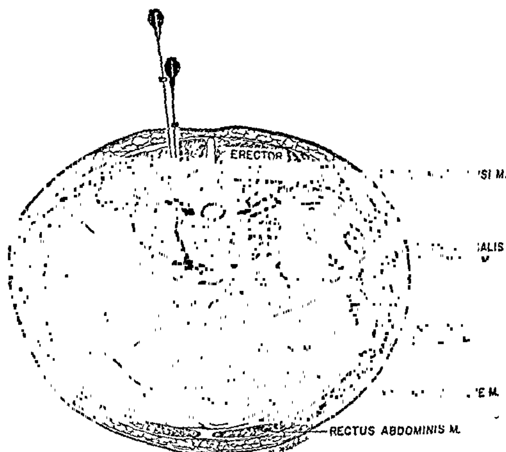


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* As the lumbar nerves lie midway between the transverse processes, the needles must be advanced slowly and their direction changed if paresthesias are produced.

CHAPTER XXI

Peripheral Sympathectomy by Crushing the Mixed Nerves in the Lower Extremity

This procedure was developed to relieve the severe rest pain which is often a major problem in the management of certain cases of thromboangiitis obliterans and arteriosclerosis. In the presence of localized ulceration or gangrene of the toes or more distal portions of the foot, these patients often suffer untold agony. Our primary purpose was to render such areas insensitive so that antiseptic dressings and postural exercises could be tolerated. This not infrequently resulted in healing as well as improvement in the general condition of the patients. They then were able to sleep without drugs and to co-operate in other forms of conservative treatment designed to improve collateral circulation.

In many instances a substantial rise in surface temperature of the denervated area was noted. Such a response is shown in Figure 107. It therefore became apparent that an actual increase in peripheral blood flow had resulted from interruption of vasomotor pathways which accompany the crushed sensory nerves. The beneficial effect of this procedure may therefore depend in part upon this peripheral form of sympathectomy. This increase in circulation, however, is never of long duration. The observations made by one of us (J. C. W.) during the last war on peripheral nerve injuries showed that the early vasodilator response was ultimately replaced by distinct cooling of the skin in the desensitized dermatomes. While lumbar sympathectomy will cause more effective and lasting increase in circulation, it has not been so successful in relieving the pain of ulceration and gangrene. Those cases which do show an increase in blood supply to the part after nerve crushing should, in our opinion, be sympathectomized before the nerves regenerate, provided healing of the ulcerated or gangrenous areas is taking place. Furthermore, all stiff, scarred, useless toes which remain should be removed through the base of the proximal phalanges, using lateral skin flaps. This type of closed amputation can be done with safety

weight off the insensitive area. As sensory loss rarely lasts beyond a few weeks and there is no need to keep the ordinary patient in bed, this is not usually a difficult matter.

If the sympathetic block need be maintained for only a few days, the procedure suggested by Thomason and Moretz (1949) may be preferable to longer-lasting chemical interruption with alcohol or phenol. By using a 16-gauge needle it is possible to thread a No. 3½ Touhy catheter, of the type employed in continuous spinal anesthesia, through the needle. After its insertion the needle is withdrawn, leaving the catheter in position. This technique is illustrated in Figure 106. A 23-gauge needle is inserted in the distal end of the catheter and used for repeated injections of procaine at three-hour intervals. Thirty thousand units of penicillin are added to the anesthetic solution to protect against infection.

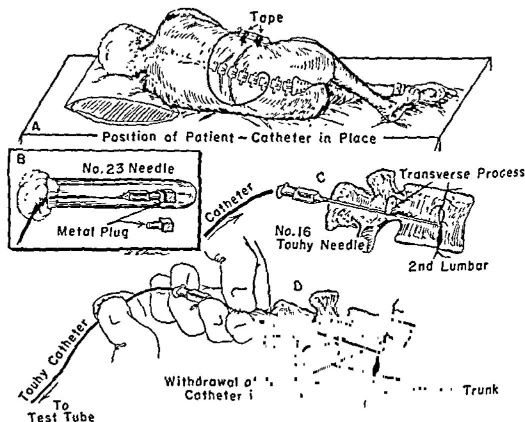


Fig. 106. Diagrammatic sketch of continuous paravertebral lumbar sympathetic block. A. Patient on side with Touhy catheter in place. B. Distal end of catheter in sterile test tube with needle inserted in catheter and metal plug in hub of needle. C. Touhy needle introduced beneath transverse process of second lumbar vertebra Catheter being inserted into the needle D Needle being withdrawn and catheter left in place. (Figure and legend reproduced from Thomason, J R., and Moretz, W. H. "Continuous lumbar paravertebral sympathetic block maintained by fractional instillation of procaine," by permission of *Surgery, Gynecology, and Obstetrics*, Chicago, 1949, 89: 447–453.)

to the muscles of the lower leg. After considerable experience with this method we found that crushing of the nerves was easier and more satisfactory than their injection with alcohol.

The neuroanatomy of the lower leg and the technique of operation have been described in detail by Smithwick and White (1930 and 1935). The positions of the five nerves which transmit sensation from the foot are shown in Figure 108. It may be necessary to block one or all of these

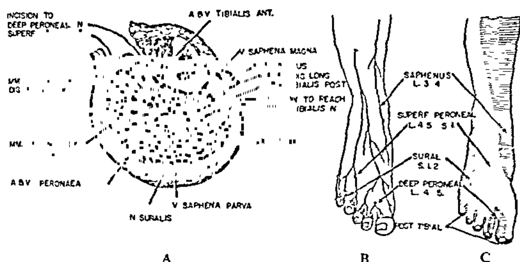


Fig. 108. Technique of exposing the mixed nerves in the lower leg. (Adapted from Homans, J. *Textbook of surgery*, 3rd ed., Charles C Thomas, Springfield, Ill., 1935.)

nerves in a given case. This should be done at a point sufficiently high to include all collateral branches which reach the painful zone, but at the same time below the motor branches to the important muscles in the leg. In general, the optimum point to accomplish this is at the junction of the middle and lower thirds of the leg (about 6 in. above the ankle). Experience with many patients has shown that small, longitudinal incisions at this level in cases of thromboangiitis obliterans will nearly always heal, provided the gangrene is confined to the distal part of the foot. First-intention healing has taken place even in the absence of any peripheral pulsations in Buerger's disease, but in arteriosclerosis this cannot always be counted on when the popliteal artery is occluded.

In order to ensure healing in legs with a poor blood supply, operations should be performed with meticulous care against trauma and sepsis. Forceps should not be used on the skin; retraction should be very gentle. It is essential to know exactly where the nerves lie so that lateral dissection and stretching of the tissues can be avoided On the rare occasions when bleeding vessels are encountered, only the finest chromic catgut ligatures

in the absence of main vessel pulsation, provided the technique is beyond reproach, all ulceration has healed, and an adequate collateral circulation has developed. To leave these superfluous toes behind is only courting future episodes of ulceration or gangrene, as lesions of this type nearly al-

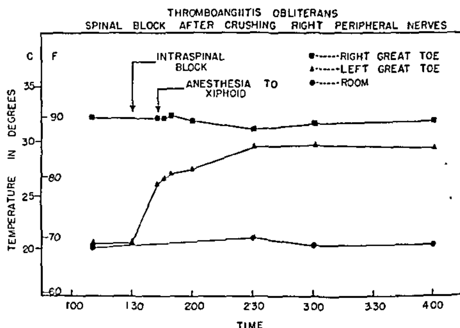


Fig. 107. Increased blood flow after crushing peripheral nerves.

Crushing the peripheral nerves resulted in an increased blood flow to the digits. Previous to crushing the posterior tibial, superficial, and deep peroneal nerves ten days before, the skin temperature of both great toes was the same The denervated great toe on the right is now 20° F warmer and its temperature fails to rise any further after high spinal anesthesia, whereas the left great toe shows a typical vasodilator response.

ways commence in a digit. Our best results in cases having these severe forms of obliterative vascular disease have followed the judicious use of peripheral nerve crushing, sympathectomy, and minor amputation of useless digits. These operative procedures have been combined with other conservative forms of treatment such as vascular exercises, careful hygiene, and elimination of the use of tobacco.

Alcohol injection of the posterior tibial nerve was performed by Silbert (1922) for relief of pain in thromboangiitis. An incision was made at the level of the internal malleolus, exposing the nerve and injecting alcohol under direct vision. Some difficulty with wound healing was encountered. It seemed to us that all of the five nerves concerned could be exposed at higher levels in the leg. By selecting the proper combination of nerves it was found possible to relieve pain completely and practically to eliminate the incidence of poor wound healing without sacrificing important motor fibers

nerve at the inner aspect of the knee and have had similar gratifying results. The sural nerve can be treated in similar fashion for painful ulcers of the lateral malleolus.

Over twenty years have passed since the procedure of crushing peripheral nerves was first used by us. At that time we were frequently confronted with late and neglected cases of obliterative vascular disease. These individuals suffered untold agony from their ulcerations, which often necessitated amputation. With the passage of time, these late and neglected cases are now seen much less frequently, so that the need for this procedure has decreased. Nevertheless, it is still very useful in selected cases. A further development in the management of obliterative vascular disease has also narrowed the indications for crushing peripheral nerves. Surgeons have gradually come to recognize the fact that closed amputations through the metatarsal bones and even through the distal portions of the tarsal bones can be performed in the presence of localized ulceration or gangrene of the digits, or even through the distal portion of the foot in the absence of main vessel pulsation. These amputations are successful in a high percentage of cases *if the collateral circulation is adequate and the operations are skillfully performed.* The results of these amputations have been reported by McKittrick, McKittrick, and Risley (1949) and the factors which influence the outcome have been discussed by Smithwick in commenting on this paper. Thus, certain patients who formerly would have been treated by peripheral nerve crushing followed by sympathectomy and a minor amputation, if necessary, are now managed by a transmetatarsal amputation preceded by sympathectomy if an active vasoconstrictor mechanism is found to be present.

The principle of desensitization by crushing peripheral nerves can be applied to the upper extremity, although the need for crushing the nerves to the hand rarely arises. We have successfully denervated painful ulcerated or gangrenous digits in the upper extremities by crushing the sensory nerves concerned. Those to the dorsum of the hand can be crushed at the wrist. The digital branches of the ulnar and median nerves can be exposed distal to their important motor outflow through small longitudinal incisions in the palm.

(0000) should be used. To avoid further foreign material in the wound, it is best not to suture the fascia; the skin should be loosely sutured with the finest silk. As a general rule only one nerve, or at most two nerves, should be exposed at a time.

Experience has shown that the simplest way to paralyze a nerve so that it can be counted on to regenerate is to crush it in a hemostat. A nerve so treated over an extent of 3 to 5 mm at the junction of the middle and lower thirds of the leg will regenerate in about three to six months. Crushing the nerves has numerous advantages over alcohol injection, which was previously recommended by us. Smaller incisions are possible, chemical irritation of the tissues is avoided, and the period of nerve regeneration is easier to control. We do not favor section and resuture of the nerves, as recommended by Laskey and Silbert (1933), as this is no more effective than simple crushing and makes the operation more complicated and difficult.

This minor procedure, when properly carried out, causes virtually no discomfort or subsequent inconvenience to the patient. He can be up in a chair after his return to the ward. The relief of pain and freedom from vasoconstriction are an enormous advantage in treating patients with thromboangiitis obliterans. The temporary motor and sensory paralysis resulting from this procedure has no serious untoward effect. Patients walk surprisingly well when the intrinsic muscles of the foot are paralyzed. Care should be taken to see that shoes fit properly to avoid ulceration from pressure. Patients should be cautioned against use of excessive heat. One patient received a severe burn from resting his denervated foot upon a hot radiator. The sensory nerves regenerate very completely. Some atrophy of the intrinsic muscles of the foot may persist, but this has not been troublesome. The operation should not be used as a treatment for vasospastic disorders. It is intended only as a means of tiding the patient over a critical period of ulceration and gangrene. It is difficult to state the results with accuracy because other forms of treatment are used as well in most of these patients. *Our impression, however, is that this operation has* doubled the number of successful minor amputations of ulcerated or gangrenous toes, and has reduced major amputations to one third of the number which was necessary before its introduction.

As a modification of our original procedure Atlas (1950) has recently advocated cutting the saphenous nerve in Scarpa's triangle for cases of painful indolent ulcers situated on the inner aspect of the leg and internal malleolus. Following this simple procedure, he reports successful relief of pain and a distinct acceleration of healing. We have usually crushed the

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Epilogue

In his classical description of the involuntary nervous system the great French physiologist, Claude Bernard, stated that "nature thought it prudent to remove these important phenomena from the caprice of an ignorant will." Now that the surgeon has entered the picture, it becomes all important that he develop a thorough understanding of neurophysiology before he undertakes to interfere with these automatic processes which control the body's adjustment to its environment. It is our hope that this book may help surgeons attain the wisdom necessary to modify, in an effective way, what Cannon has called "the wisdom of the body," when disease makes such regional readjustments advisable.

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INDEX

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